Lacunar brain infarcts : a clinical and pathogenetical study

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LACUNAR BRAIN INFARCTS

A Clinical and Pathogenetical Study

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"Every intellectual has a very special responsibility... he owes it to his fellow men (or to 'society') to represent the results of his study as simply, clearly, and modestly as he can. The worst thing he can do - the cardinal sin - is to try to set themselves up as great prophets vis-a-vis their fellow men and to impress them with puzzling philosophies. Anyone who cannot speak clearly should say nothing and continue to work until he can do so".

Karl Popper (1902-1994), philosopher of science, in his essay "Against big words'.

Ter nagedachtenis aan mijn vader
Voor Birgit

List of abbreviations

(a)OR	=	adjusted Odds Ratio
(c)OR	=	crude Odds Ratio
ACA	=	AntiCardiolipin Antibodies
ACE	=	Angiotensin-Converting Enzyme
AF	=	Atrial Fibrillation
AH	=	Ataxic Hemiparesis
APC	=	Activated Protein C
CADASIL	=	Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leucoencephalopathy
CI	=	Confidence Interval
CT	=	Computer Tomography
DM	=	Diabetes Mellitus
HAH	=	Hypaesthetic Ataxic Hemiparesis
HLA	=	Human Leucocyte Antigen
IH	=	Isolated Hemiataxia
IHD	=	Ischaemic Heart Disease
LAC	=	Lupus AntiCoagulant
MBIR	=	Maastricht Brain Infarct Registry
MRI	=	Magnetic Resonance Imaging
NS	=	Not Significant
RBF	=	Renal Blood Flow
SEP	=	Somatosensory Evoked Potentials

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General introduction

Lacunar infarcts are small infarcts, located deeply in the brain or brainstem (43). They usually result from the occlusion of a single small, deep perforating artery and they manifest with several syndromes, the so-called lacunar syndromes. This clinicopathological concept was (43,46,54,55) introduced in the sixties by Fisher, and sustained by others (7,8,17,78). Lacunar stroke may therefore be considered as a separate stroke entity with characteristic clinical features, and a distinctive pathogenesis. However, some specific questions on lacunar stroke remain and require further study (chapter 1).

The patients studied in this thesis were selected from the Maastricht Brain Infarct Registry. A brief description of this registry and the patients profile are given in chapter 2.

It is unknown whether the vasculopathy of the small vessels in lacunar stroke is limited to the brain, or whether it is part of a more generalised extra-cerebral small-vessel disease. Extra-cerebral small vessels, for example in the retina, nailfold and kidney, are more easily accessible for investigation than cerebral small vessels. Therefore, studying manifestations of vascular disease in lacunar stroke patients might give more insight in the nature of the vasculopathy underlying lacunar stroke. This is studied in chapter 3.

Clinical studies demonstrated that the vascular risk profile in lacunar and cortical stroke is similar (17,21,95). What causes either stroke subtype in the same atherogenic conditions remains unknown. Haemostatic abnormalities or a genetic predisposition may play a role in the development of lacunar infarcts. In chapter 4 we studied haemostatic disorders in lacunar stroke. To study a possible genetic predisposition in lacunar stroke Human Leucocyte

Antigen (HLA) typing in patients with lacunar stroke was performed. The results are described in chapter 5.

Ischaemic stroke is often considered a disease of the elderly, but stroke below the age of 50 is not uncommon, and accounts for up to 10% of all strokes (35). The major cause of ischaemic stroke among the elderly is atherosclerosis and to a smaller extent cardioembolism, mostly related to nonrheumatic atrial fibrillation. However, the causes of ischaemic stroke in patients below the age of 50 are more diverse. Unusual causes need to be considered, such as carotid artery dissection, valvular and congenital heart disease, vasculitis and coagulation disorders. Special ancillary tests in search for such specific or "rare" causes are often necessary. It is not known whether the "rare" stroke causes occur in both lacunar and nonlacunar young stroke patients, or whether they are limited to one of these stroke subtypes. If "rare" causes would be confined to one stroke subtype, this may have implications for performing ancillary tests. In chapter 6, we investigated the presence of "rare" causes in lacunar and in nonlacunar stroke in both young and elderly patients.

Hemiataxia is one of the neurological signs which may occur after lacunar infarction. Usually, hemiataxia after lacunar infarction is part of the lacunar syndrome of ataxic hemiparesis. This syndrome consists of hemiparesis and ataxia on the same side of the body (48,54). Isolated hemiataxia after supratentorial lacunar infarction is very rare, and has only been described once after a lacunar infarct in the thalamus (52). In chapter 7, 3 patients with isolated hemiataxia following lacunar infarction are described.

There is controversy in the literature concerning the cause of ataxia following lacunar infarcts. Ataxia may be cerebellar resulting from interruption of the cerebellar pathways (18,48,51), or sensory due to disturbed proprioception, as supported by reported abnormal somatosensory evoked responses (SEP) in a few patients (83,111). Therefore, in chapter 8, a consecutive series of patients with ataxia following lacunar infarcts were studied with sensory testing and SEP in order to explore the cause of ataxia.

In summary:

This thesis aims to answer the following questions:

1. Is the cerebral small-vessel disease in lacunar stroke patients restricted to the brain, or is it part of a more generalised small-vessel disease? (chapter 3)

2. Are there haemostatic disorders in lacunar stroke? (chapter 4)

3. Is there a possible genetic predisposition for lacunar stroke? (chapter 5)

4. Does lacunar stroke, like cortical stroke, have a variety of "rare" causes among young stroke patients? (chapter 6)

5. What is the clinical-topographical relationship of isolated hemiataxia in patients with lacunar infarction? (chapter 7)

6. Does cerebellar or sensory dysfunction cause the ataxia following lacunar infarction? (chapter 8)

Chapter 1

Introduction

Lacunar infarcts

Lacunar infarcts are small ischaemic infarcts located deep in the brain or brainstem (43) and represent approximately 25% of all first-ever brain infarcts (7). They are usually caused by occlusion of a single small, deep, perforating artery, and can usually be recognized from a limited number of clinical syndromes, the so-called lacunar syndromes (8,46). The perforating arteries are endarteries which lack collaterals, although some anastomoses have been described (146). Lacunar infarcts range in size from 3 to 15 mm (43). The larger lacunar infarcts tend to be more often symptomatic, whereas the smaller ones are only symptomatic when located in neurologically strategic brain areas. Lacunar infarcts are mainly located in the putamen, caudate nucleus, thalamus, pons, internal capsule and corona radiata (51).

On CT scan lacunar infarcts are visible as small, sharply delineated, hypodense lesions without mass effect (149). CT scan visualized two-third of the infarcts in patients clinically suspected of lacunar stroke (17). Sequential high resolution scanning with thin slices improves the detection rate of lacunar infarcts, but in about one-fifth of patients with the clinical suspicion of a lacunar infarct the ischaemic lesion remains undetected (82). On MRI lacunar infarcts are visible as small, high signal intensity lesions on T2-weighted images, and as low signal intensity lesions on T1-weighted images (73). MRI has proven to be superior to CT scanning in detecting lacunar infarcts, especially in the acute stage, and in detecting lacunar infarcts located in the posterior fossa (73,122,124). Although MRI is more sensitive than CT, it has a lower specificity: differential pathological processes, such as gliosis, myelin loss, and lacunes may produce similar images (73).

Vascular risk factors and pathogenesis

Recent studies on vascular risk factors in lacunar stroke were mainly undertaken to clarify the underlying vascular abnormalities in lacunar infarction. Because of low early case fatality rate, pathological studies are difficult to perform in lacunar infarction, and insight into the pathogenesis in lacunar infarction might come, although indirectly, from comparison of the vascular risk profile and potential stroke causes between lacunar infarction and other brain infarct subtypes. Studies on vascular risk factors in lacunar infarction were reviewed recently (21). The established vascular risk factors for lacunar stroke are age and sex, hypertension, diabetes mellitus, ischaemic heart disease, transient ischaemic attack (TIA) and cigarette smoking.

The frequency of hypertension in lacunar stroke varied between 44 and 75%. Differences in definition of hypertension and study methods may explain this variation in frequency. Compared to controls without stroke, hypertension was found more often in patients with lacunar stroke (75% vs 35% and 65% vs 30%) (58,98). In clinical studies comparing lacunar with nonlacunar stroke patients, no significant difference was found in the frequency of hypertension between both groups (17,96,120). These data did not confirm Fisher's original suggestion that hypertension was the sole important risk factor for cerebral small-vessel disease causing lacunar infarction. However, some investigators still ascribe a major role to hypertension in the cause of lacunar infarction (12). In summary, hypertension is an important but rather nonspecific and not unique vascular risk factor in lacunar stroke, as it is in other stroke subtypes.

Similar conclusions can be drawn concerning diabetes mellitus, a history of ischaemic heart disease, previous TIA and smoking (21). Possible other risk factors for lacunar stroke are hyperlipidaemia, increased haematocrit, lower limb claudication, hyperhomocysteinaemia, fibrinogen, and excessive alcohol consumption. These risk factors are more or less established for ischaemic stroke in general, but not for lacunar ischaemic stroke specifically (21).

Based on his few, but meticulously performed pathological studies, Fisher distinguished two types of small-vessel vasculopathy in lacunar stroke. In *microatheromatosis*, the most common small vessel vasculopathy, a small atheromatous plaque narrows or occludes the perforating artery proximally at its orifice, mainly affecting vessels larger than 200 micron (46,50). The histological characteristics seem similar to those in large vessel atherosclerosis. Microatheromatosis is believed to cause single, larger, usually symptomatic lacunar infarcts (27,46,47,49,53). *Lipohyalinosis* causes small, multiple, and usually asymptomatic, lacunar infarcts (46). Lipohyalinosis is characterised by segmental disorganization of the vessel wall in which muscle fibres and subintimal hyaline material are replaced by fibrinoid and collagen deposits. Mainly the smaller vessels, below 200 microns, are affected (47). Lipohyalinosis is related to hypertension, and thought to be an intermediate state of fibrinoid necrosis in severe hypertension. Fibrinoid necrosis is found in patients with 'malignant' hypertension, and is not limited to the brain but is also found in other parts of the body, such as the retinal and renal arteries (29).

Other pathogenetic mechanisms in lacunar infarction have been proposed, such as embolism, either from the heart or from the carotid artery (59,98,114,119,125). However, clinical studies demonstrated that patients

with lacunar stroke had significantly less potential cardioembolic sources than nonlacunar stroke patients (21,95). In a case-control study, patients with lacunar stroke had a similar frequency of nonrheumatic atrial fibrillation as controls without ischaemic stroke (58). Carotid artery-to-artery embolism is considered as one of the main causes of cortical stroke. In comparison with lacunar stroke, internal carotid stenosis of more than 50% was significantly more frequent in cortical stroke (17). Probably, emboligenic heart disease and carotid stenosis are merely indicators of generalised vascular disease, and not directly related to the cause of lacunar stroke in most patients. Cardiac and carotid embolism are *unlikely* but not impossible causes of lacunar infarction.

A clinical study hypothesized that the two pathologically defined small-vessel vasculopathies manifest differently during life: patients with multiple lacunar infarcts (mostly asymptomatic) and a high incidence of hypertension and leukoaraiosis may have lipohyalinosis, whereas those with a single, symptomatic lacunar infarct and usually without leukoaraiosis may have microatheromatous disease (20). This hypothesis was recently supported by others (103).

It is unknown whether cerebral small-vessel disease is restricted to the brain or whether it is part of a more generalised extra-cerebral small-vessel disease. Extra-cerebral small-vessels are more easily accessible for investigation than cerebral small-vessels, for example retina photographs, capillary microscopy of the nailfold and functional investigations of the kidney. The occurrence of vascular changes in lacunar stroke patients of small vessels in the retina, nailfold and kidney may support the diagnosis of generalised small-vessel disease on the one hand, and on the other hand it may provide more information on the nature of the cerebral vasculopathy in lacunar stroke.

In approximately 1% of all patients and in up to 4% of young adults with ischaemic stroke, primary haematological disorders are the cause of the cerebral infarct (66). These disorders include qualitative and quantitative disorders of platelets and erythrocytes, and a number of acquired and hereditary forms of hypercoagulability (thrombophilia) such as deficiencies of coagulation inhibitors: antithrombin, protein C and protein S, antiphospholipids antibodies, homocysteinaemia and impaired fibrinolysis. Recently a new hereditary disorder of blood coagulation has been described, the so-called activated protein C (APC) resistance, which appeared to be due to a mutation in coagulation factor V (factor V Leiden) (10,34,134). Activation of other haemostatic parameters has frequently been described

during the acute phase of stroke. These abnormalities include enhanced fibrin formation (enhanced thrombin activity), abnormal fibrinolysis and platelet dysfunction. Controversy still exists whether these (secondary) changes are part of the acute phase response to the thrombotic event or causally related to the ischaemic stroke (84). In recent years, the possible role of prothrombotic states in synergy with vascular disease in the pathogenesis of cerebrovascular occlusive disease has gained more attention (66,104). Abnormalities of the coagulation system, resulting in enhanced thrombin activity, may contribute to ischaemic stroke by lowering the threshold of thrombogenesis in the presence of an underlying vascular pathology.
Several studies have focused on the haemostatic abnormalities in both lacunar and cortical stroke (40,56,135,136). The results of these studies are controversial, but suggested that these haemostatic abnormalities are confined to cortical stroke. However, in some of these studies the comparison between the stroke subgroups was based on post hoc analysis (40,56). In a recent small study (84), haematologic abnormalities were reported in both lacunar and cortical stroke.

Genetical aspects

The established vascular risk factors only partially account for the risk of lacunar stroke. Other factors may be involved in the cause of lacunar stroke, such as genetical factors. Hypertension and diabetes are under genetic influence, and are examples of so-called "complex" genetic disorders. Complex genetic disorders are thought to be due to multiple gene interactions influenced by environmental factors with a variable clinical expression of the disease phenotype (4). Other, as yet unspecified genetic factors may be involved in cerebrovascular disease. The importance of genetic factors in vascular disease has been illustrated in ischaemic heart disease. Having an affected first degree relative younger than 55 years increases the risk for ischaemic heart disease by tenfold in first degree family members (4,113). A family history of vascular disease affects the risk of ischaemic stroke, but not as impressive as in ischaemic heart disease (24). Direct comparison between ischaemic heart disease and ischaemic stroke is difficult, because stroke is clinically and etiologically more heterogenous. Besides "complex" genetic disorders, "simple" genetic disorders, which are due to a single-gene defect following a Mendelian pattern of inheritance (4), could be studied. A single-gene defect causing a specific stroke type might give more insight into the cause and pathogenesis of this stroke type and allow analysing stroke in general. Single-gene diseases that specifically and directly affect the cerebral small vessels are very rare. Dutch and Icelandic amyloid angiopathy are

examples of single-gene diseases affecting predominantly the superficial small vessels of the brain. Both diseases present primarily with intracerebral haemorrhages, not with infarction. Recently, a rare genetic stroke syndrome involving the small deep vessels of the brain has been reported (23). This syndrome is called CADASIL: an acronym for Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy. CADASIL patients present with recurrent lacunar strokes or TIA's in the 3th and 4th decade of life. Migraine-like headache and depression may also be present. After several years the clinical picture of the disease alters into steadily progressive pseudobulbar palsy, subcortical dementia, and cerebellar signs. Neuroimaging shows small deep (lacunar) infarcts and widespread white matter lesions (leukoencephalopathy). The disease locus has been assigned to chromosome 19q12 in two unrelated French families (142).

What determines whether small vessels or large vessels will become affected in the presence of the same atherogenic circumstances, remains unknown. A possible, until now unknown, genetic predisposition to develop either small or large-vessel disease may be present. It is known that the genetic inheritance and expression of certain Human Leukocyte Antigens (HLA) place an individual at an increased risk of various diseases (141). Therefore, it would be of interest to study HLA frequencies in lacunar stroke patients to investigate a possible genetic predisposition for cerebral small-vessel disease.

Lacunar stroke in young patients

Ischaemic stroke is often considered a disease of the elderly. However, up to 10% of all strokes occur in persons below the age of 50 (35). Most cases of stroke in the young appear to be ischaemic, although the relative proportion of haemorrhages is larger than in the elderly (99). The incidence rate of ischaemic stroke in patients between 15 and 45 years ranges between 2.0 and 15.5 per 100.000 per year (99). In the population based-primary stroke centres of Lausanne and Maastricht, 12 and 8% respectively of all patients with a first ischaemic stroke were younger than 45 years (14). In an East-Asian hospital series, 16% of all patients with a first ischaemic stroke were 50 years or younger (101), mostly as a consequence of rheumatic heart disease. The incidence of lacunar stroke in the young is not known. In 2% of all patients from the Laussane stroke registry with ischaemic stroke younger than 45 years, small-vessel disease associated with hypertension was presumed (14). In the Iowa, and Lisbon registries of ischaemic stroke in young adults, in 8.0 and 9.6% lacunar stroke was diagnosed (3,42).

The spectrum of causes of ischaemic stroke in young patients is more diverse than in elderly patients. In general, young patients have a relatively high frequency of unusual or "rare" causes, unlike the elderly, in whom atherosclerosis is by far the most frequent cause of ischaemic stroke. More than 100 potential causes have been reported (14,67). It is difficult to provide an accurate hierarchy of causes of ischaemic stroke in the young, because the reported series can hardly be compared due to differences in patient selection, diagnostic criteria and tests performed. In a varying proportion of 5 to 65%, the cause of ischaemic stroke in the young remains undetermined (147). The most common causes of ischaemic stroke in the young are listed in order of frequency in table 1.

Generally, an aggressive search for a cause in young stroke patients is advocated (148). Angiography is regarded as mandatory in the evaluation of young stroke patients if no obvious cause is present (2). In the past years, some new developments have emerged in the evaluation of young stroke patients. New techniques such as transesophageal and contrast echocardiography might increase the number of strokes which can be attributed to cardiac disorders. However, these investigations may identify an increasing number of possible cardioembolic sources such as mitral valve prolapse, patent foramen ovale, and atrial septal aneurysm, which are not uncommon in healthy young adults (74). These possible cardioembolic sources may be largely incidental findings rather than the cause of stroke. Similarly, ischaemic stroke has been attributed to the antiphospholipid antibody syndrome. However, the role of this new disorder as cause of ischaemic stroke in the young remains controversial (14,112). More studies (e.g. case-control) to demonstrate an definite etiological role of the antiphospholipid antibodies in ischaemic stroke in the young are required.

Table 1

Causes of ischaemic stroke in patients less than 50 years of age

1. Atherosclerosis		
	- especially > 30 years, with known vascular risk factors	**20-35%**
	- premature atherosclerosis - rare inherited disorders hyperhomocysteinaemia dyslipidemia Tangier disease Fabry disease	
2. Cardioembolic		
	- valvular disease rheumatic heart disease congenital prosthetic endocarditis mitral valve prolapse	**10-30%**
	- cardiomyopathies	
	- myxoma	
	- paradoxical embolism patent foramen ovale atrial septal defect atrial septal aneurysm	
	- arrhythmias atrial fibrillation (rare) sick sinus syndrome (rare)	
	- myocardial infarction	
3. Cervicocephalic arterial dissection		
	- spontaneous	**10-20%**
	- fibromuscular dysplasia	
	- neck trauma	
	- Marfan disease;type IV Ehlers- Danlos	
4. Coagulopathy		
	- primary antithrombin deficiency protein C/S deficiency antiphospholipids antibodies APC-resistance?	**5%**
	- secondary oral contraceptives pregnancy/peripartum hyperhomocysteinaemia	
5. Small-vessel disease		**2-8%**
6. Possible causes		
	- migraine	**10-35%**
	- alcohol intoxication	
7. Undetermined		**5-65%**

Since the causes of ischaemic stroke in the young are diverse, it remains difficult to provide an accurate algorithm for the evaluation of these patients. A careful individual evaluation of young stroke patients is recommended, because exhaustive diagnostic tests applied to every young stroke patient, regardless of clinical features or stroke subtype, can be questioned (3).
It is not known whether these "rare" and specific disorders in young patients may cause both lacunar and cortical stroke, or whether they only cause one of these stroke subtypes. If these "rare" causes would largely be confined to cortical stroke patients, they would support the concept that lacunar infarcts are the result of a distinctive cerebral small-vessel disease, which may be independent of age. Such a finding may have implications for the management of young lacunar stroke patients. Not only the need of sophisticated cardiac investigations in these patients may be questioned, but also duplex scanning of the carotid artery and cerebral angiography in search for specific vascular disorders, such as carotid artery dissection and vasculitis, may be redundant.

Ataxia in lacunar stroke

Fisher has described that patients with lacunar stroke had certain distinctive clinical symptoms and signs. These so-called "lacunar syndromes" are composed of focal symptoms and signs, present at the time of maximal deficit, following a single, focal cerebrovascular event (7,44,45,51, 54,55,97). The presence of a visual field deficit or cortical dysfunction (e.g. dysphasia, visuospatial disturbance, apraxia, agnosia or neglect) or features that clearly localize the lesions to the brain stem (except dysarthria and nystagmus) exclude the diagnosis of a lacunar syndrome (7,96). Since Fisher introduced the concept of lacunar syndromes in the sixties, he has reported on more than 60 lacunar syndromes (52). However, only the first 4 reported lacunar syndromes of pure motor stroke, sensorimotor stroke, pure sensory stroke and ataxic hemiparesis (including dysarthria clumsy hand syndrome) have a solid pathological evidence. The other miscellaneous lacunar syndromes are rare, consist mostly of single cases, and lack a solid clinicopathological correlation.

Ataxic hemiparesis is the lacunar syndrome that has probably generated more debate than the other 3 lacunar syndromes (94). This syndrome was first described by Fisher and Cole in 1965 as the syndrome of *"homolateral ataxia and crural paresis"* (54). They reported 14 patients, who all had leg weakness and more prominent homolateral ataxia of the arm, with little or no involvement of the face. Later, when ataxia was found with hemiparesis in

the arm as well as in the leg, Fisher introduced the term *"ataxic hemiparesis"* (48). Slight hypaesthesia might be part of this syndrome. *"Dysarthria-clumsy hand"* syndrome, which is regarded as a variant of ataxic hemiparesis (45,51), exists of facial weakness, severe dysarthria and dysphagia combined with a slight weakness and clumsiness of the hand. Bamford et al. (7) defined ataxic hemiparesis as ipsilateral corticospinal and cerebellar-like dysfunction, without other features that clearly localize the lesion to the posterior circulation. This includes cases with predominantly dysarthria and clumsiness of the hand. Ataxic hemiparesis as a separate lacunar syndrome has been questioned because most patients with hemiparesis are more or less ataxic (90). However, a striking clinical finding in these patients is that the ataxia is out of proportion to the degree of weakness. Moreover, in many patients with ataxic hemiparesis the hemiparesis resolves, while the ataxia remains. (48,52). The frequency of ataxic hemiparesis in comparison with the other lacunar syndromes varies in CT scan studied series from 1 to 16%. (7,17,37,53,149). There are only a few post mortem studies on ataxic hemiparesis, which found infarcts in the internal capsule, the thalamus and the upper pons (48,54). CT and MRI also showed infarcts in the corona radiata, the anterior limb of the internal capsule extending to the head of the caudate nucleus, the posterior limb of the internal capsule extending to the thalamus, the ventrolateral nucleus of the thalamus, and in the median and lower part of the pons (15,26,36,63,69,121). The basis of the pons is thought to be the infarct site causing a dysarthria-clumsy hand syndrome, although sporadic lacunar infarcts have been reported in the corona radiata and internal capsule (61). Ataxic hemiparesis has also been described in patients with cortical infarcts, for instance in the territory of the anterior cerebral artery (13), and in small haemorrhages in the thalamus, pons, or the internal capsule (111,128,129).

Some patients with ataxic hemiparesis have also prominent sensory disturbances, the so-called *hypaesthesic ataxic hemiparesis* (91). In a series of 23 patients with hypaesthesic ataxic hemiparesis, all but one had a lacunar infarct in the contralateral posterior limb of the internal capsule (68). Isolated hemiataxia and ipsilateral sensory loss without hemiparesis, *hemiataxia-hypaesthesia*, has been reported in lacunar infarcts in the lateral part of the thalamus (105). *Isolated hemiataxia* has only once been described after thalamic infarction (52). Obviously, there is a variety of ataxic syndromes following lacunar infarcts in a variety of locations. Therefore, controversy exists concerning the exact cause of the ataxia in the syndromes of ataxia following lacunar stroke. Ataxia may result from cerebellar dysfunction (cerebellar ataxia), or from disturbed proprioception (sensory ataxia). Fisher and others (18,48,54) described ataxia in ataxic hemiparesis as cerebellar-

like, because they found normal proprioceptive sensory modalities on clinical testing, whereas eye-closure did not worsen the ataxia. Interruption of the cerebellar pathways, either the ascending dentatorubrothalamocortical or descending corticopontocerebellar pathways may explain the cerebellar-like ataxia. Such interruption can occur at the level of the internal capsule, the upper pons or the corona radiata (48,54,75). Others suggested disturbed proprioception, resulting from damage to the lateral thalamus and/or thalamocortical sensory projections, as the cause of ataxia, sustained by abnormal somatosensory evoked responses (SEP) (83,111).

SEP and ataxia in lacunar stroke

Somatosensory evoked potentials (SEP) are recorded centrally after stimulation of peripheral sensory nerves. SEP reflect the integrity of the proprioceptive system, particularly of the large fibre sensory pathways, traversing the posterior columns, through the medial lemnisci to the contralateral thalamus reaching the frontoparietal sensorimotor cortex. There is a close relation between wave forms and the anatomy of sensory pathways, allowing precise localisation of conduction defects (30,31). SEP may also be used to detect subclinical affliction of sensory signal conduction. A few SEP studies in patients with lacunar stroke have been performed (1,6,32,83,89,111,114,120). About 40% of the patients in these studies had an abnormal SEP. The SEP abnormalities consisted of latency and/or amplitude differences of the peaks between both hemispheres, and of absence of the peaks in the affected hemisphere. There was no relation between clinical features and an abnormal SEP. Curiously, most patients with pure sensory stroke have normal SEP, whereas some patients with pure motor stroke had abnormal SEP. A possible explanation for these findings is that the infarct size may be critical in generating abnormal SEP. The infarcts causing pure sensory stroke are often the smallest of lacunar infarcts (73,120), whereas infarcts causing pure motor stroke are usually larger (109,120). A pure motor stroke generating abnormal SEP suggests a subclinical involvement of the sensory system in this lacunar syndrome. Others suggested that abnormal SEP did not depend on infarct size but on infarct location. Especially infarcts in the thalamo-capsular region could cause abnormal SEP (1).

The SEP studies (1,5,83,89,111) in ataxic hemiparesis comprised only 15 patients in total, including 3 patients with a small haemorrhage in the posterior limb of the internal capsule (111). Ten of the 15 patients had abnormal SEP, such as latency or amplitude differences of the peaks between both hemispheres, or absence of peaks to the affected hemisphere. SEP

abnormalities in ataxia hemiparesis did not differ from the other lacunar syndromes. In two studies, which dealt exclusively with ataxia and SEP, all 7 patients had abnormal SEP and the authors suggested proprioceptive deficits as the cause of ataxia (83,111).

All these different studies included small numbers of patients and the results may represent the effect of selective sampling. Therefore, it would be of interest to study clinical sensory testing and SEP in a consecutive series of patients with ataxic hemiparesis following lacunar stroke to unravel the cause of ataxia, and to gain more insight into the clinical-topographical aspects of ataxia in lacunar infarcts.

Chapter 2

Maastricht Brain Infarct Registry

The Maastricht Brain Infarct Registry (MBIR) is a prospective registry at the University Hospital of Maastricht of all patients of 15 years or older with a supratentorial first-ever brain infarct with symptoms and signs lasting longer than 24 hours. It was started in July 1987 and collects information of an adherent population of approximately 190,000 people. Although the registry is hospital-based, we suspect no major bias in patient sampling, because the hospital is the only hospital in the Maastricht area. Patients admitted to the hospital as well as those visiting the outpatient clinic are registered. In the Netherlands patients with a stroke are usually admitted during the acute phase of the stroke (85% of all stroke-patients with even an higher incidence in first-ever cases (71)), whereas the remaining patients are likely to visit the out patient clinic. In addition, patients not seen at the hospital are most likely those with rapid disappearance of symptoms and those who die early, representing TIA and cerebral haemorrhage, respectively, which are not included in the registry. All patients were examined as soon as possible after admission or at the first out patient clinic visit. They had routine investigations including standard blood and urine tests, a 12-lead electrocardiogram (ECG), a chest X-ray, non-invasive carotid studies and CT scan or MRI. Non-invasive carotid studies consisted of multi-gate pulsed Doppler with spectral frequency analysis, duplex scanning, or continuous-wave Doppler. Echocardiography, 24-hours (Holter) monitoring, and cerebral angiography were performed in selected patients.
Patients' data were registered on standardised forms (see appendix at the end of this chapter).

Definitions

A brain infarct or *ischaemic stroke* was defined as rapidly developing clinical signs of focal disturbance of cerebral function, lasting longer than 24 hours or leading to death, with no other apparent cause than a vascular origin; CT scan or MRI showed a lesion compatible with the clinical signs and symptoms or was without specific lesion. When neither CT, MRI, or autopsy were available, we used the Guy's Hospital Stroke Diagnostic Score (Allen Score) that predicts with probability of more than 90% whether the stroke was due to an infarction when the score is lower than 4 (5).

Two ischaemic stroke subtypes were distinguished:
Lacunar stroke was defined as an acute stroke syndrome with a CT lesion compatible with the occlusion of a single perforating artery, i.e. a subcortical, small, sharply demarcated hypodense lesion with a diameter less than 20 mm, or clinically, when no specific lesion was visible on CT, using

the established criteria of unilateral motor and/or sensory symptoms and signs that involved the whole of at least two of three body parts (face, arm, leg) without disturbance of consciousness or language, visual field defect or other signs of cortical dysfunction.

Cortical stroke was diagnosed as an acute stroke syndrome with CT findings compatible with infarction involving the cortex, or clinically, when no specific lesion was visible on CT, on the basis of unilateral motor and/or sensory symptoms and signs in combination with signs of cortical dysfunction with or without a visual field defect; or incomplete involvement of two bodyparts; or isolated monoparesis (16); or isolated cortical dysfunction (usually dysphasia). Patients with a large subcortical infarct were included in this group because of similar pathogenesis (19).

The following ischaemic stroke causes were distinguished:

Small-vessel occlusion was presumed in patients who had lacunar stroke, except when they had a "rare definite stroke cause".

Large-vessel atherosclerosis was diagnosed in cortical stroke patients in the absence of a potential cardiac source of embolism or a rare stroke cause, irrespective of the degree of stenosis of the large intracranial or extracranial (carotid) arteries. We made no effort to distinguish between in situ thrombosis and artery-to-artery embolism.

(Possible) cardioembolism was diagnosed in cortical stroke patients in the presence of one of the following potential cardiac sources of embolism: atrial fibrillation (chronic, paroxysmal), recent myocardial infarction (less than 6 weeks), prosthetic aortic or mitral valve, endocarditis, cardiomyopathy, mitral stenosis, left ventricular aneurysm, and intraventricular thrombus. Patients with a potential cardioembolic cause and large-vessel atherosclerosis on duplex imaging or angiography were classified as cardioembolic. Patients with a lower-risk cardioembolic source, such as a patent foramen ovale, were only included in this category in the absence of another potential stroke cause.

A category "*rare definite stroke causes*" included patients with lacunar or cortical stroke who had a rare stroke cause, like for instance carotid artery dissection, fibromuscular dysplasia, vasculitis, or coagulation disorders.

In addition to age and sex, the following vascular risk factors were determined:

Hypertension was defined as known, treated hypertension, or two or more blood pressure recordings of >160/90 mmHg before stroke or at least one week after stroke.

Diabetes mellitus: known diabetes treated with diet and/or medication, or either fasting serum glucose >7 mmol/l or a postprandial serum glucose level > 11 mmol/l measured on at least two separate occasions before or after stroke, but not in the acute phase (the first 72 hours).

Hypercholesterolaemia: fasting cholesterol >6.5 mmol/l measured at on least two separate occasions before or after stroke.

A history of *ischaemic heart disease was* defined as myocardial infarction, angina pectoris or typical ECG changes of myocardial ischaemia.

Smoking: daily cigarette smoking

Significant carotid stenosis: diameter reduction of more than 50% of the ipsilateral (symptomatic) carotid artery on non-invasive carotid investigations or angiography.

Patients profile

In the study period between July 1987 and February 1994 899 patients were registered, 460 men (51%) and 439 women (49%), with a median age of 71 (range 15 to 96). Table 1 shows some patients characteristics and the frequency of 3 vascular risk factors for all stroke patients in comparison with a control cohort from the Maastricht region without symptomatic stroke (matched for age groups and sex). Vascular risk factors in controls have been collected in a registration network of family practices in the Maastricht region, which was described in detail recently (107).

Table 1

Frequency of vascular risk factors in the patients in the Maastricht Brain Infarct Registry and a control cohort from the Maastricht region without symptomatic stroke matched for age groups and sex. Within parentheses the percentages of findings in patients and controls.

Age Groups		N	Hypertension		DM		IHD	
			Patients	Controls	Patients	Controls	Patients	Controls
15-<45	♂	19	5 (26)	0 (0)	4 (21)	0 (0)	4 (21)	0 (0)
	♀	15	1 (7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
45-64	♂	133	62 (47)	17 (13)	15 (11)	4 (3)	36 (27)	2 (2)
	♀	62	31 (50)	3 (5)	18 (29)	0 (0)	10 (16)	0 (0)
65-74	♂	174	71 (41)	21 (12)	21 (12)	11 (6)	62 (36)	15 (9)
	♀	135	75 (56)	36 (27)	37 (27)	18 (13)	37 (27)	7 (5)
> 75	♂	134	40 (30)	19 (14)	23 (17)	16 (12)	38 (28)	15 (12)
	♀	227	129 (57)	63 (27)	65 (28)	23 (10)	58 (26)	30 (13)
Total		899	414 (46)	159 (18)*	183 (20)	72 (8)*	245 (27)	69 (8)*

*$p < 0.01$

The frequency of the 3 vascular risk factors is significantly higher in the stroke group. These findings are in agreement with previous studies (58,98). Different pathophysiologically defined brain infarct subtypes can be distinguished, such as lacunar stroke presumably due to small-vessel occlusion, and cortical stroke mostly due to large-vessel atherosclerosis or cardioembolism. Besides lacunar and cortical stroke a small stroke subgroup with "rare definite stroke causes" can be distinguished. 287 patients (32%) had a lacunar stroke, with a median age 68 (range 26-95), and 582 patients (65%) a cortical stroke, with a median age 73 (range 24-96). The subgroup with other rare definite causes consisted of 30 patients (3%), median age 64, (range 15-82). Table 2 and the figure show the frequency of vascular risk factors in lacunar and cortical stroke patients in comparison with the controls. Because of the diversity of causes in the subgroup "rare definite causes", comparison with stroke subtypes and controls was not performed.

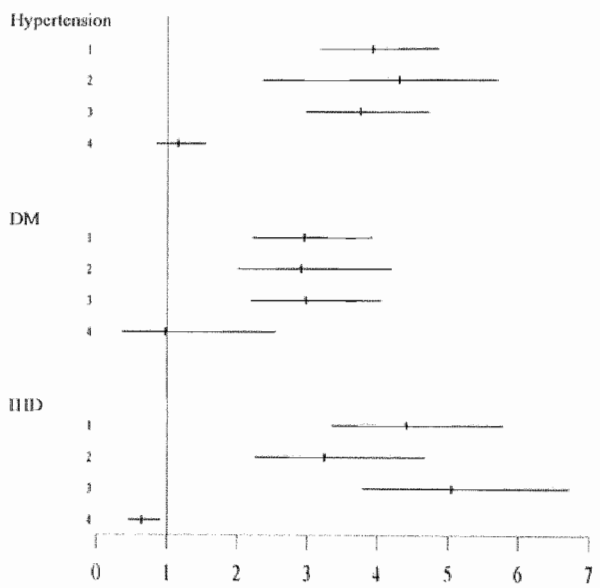
Table 2

Vascular risk factors in patients with lacunar or cortical stroke and controls. Within parentheses the percentages of findings in patients and controls.

	Lacunar Stroke N = 287		Cortical Stroke N = 582		Controls N = 899	
Hypertension	138	(48)	260	(45)	159	(18)
DM	58	(20)	120	(21)	72	(8)
IHD	61	(21)	172	(30)	69	(8)

Figure 1

Comparison of vascular risk factors in patients with lacunar or cortical stroke and controls.



Odds ratios with 95% Confidence Intervals

The results are expressed as Odds Ratio (OR) with 95% confidence intervals (CI). OR is 1.0 means equal risk for both groups. If the 95% CI include 1.0, the difference between both groups is not statistically significant (at the p =0.05 level).
1. All stroke patients vs controls; 2. Lacunar stroke patients vs controls;
3. Cortical stroke patients vs controls; 4. Lacunar stroke patients vs cortical stroke patients.

Frequency of vascular risk factors was significantly higher in the total group of all stroke patients and in both stroke subtypes as compared to controls. Lacunar stroke patients had less often a history of ischaemic heart disease than cortical stroke patients. Frequency of the remaining vascular risk factors did not differ. These findings demonstrate that these risk factors are important but not specific and not unique for either lacunar and cortical stroke, which agrees with previous studies (21). However, the frequency of a significant carotid stenosis, the presence of a potential cardioembolic source, or whether CT confirmed an infarct differed between lacunar and cortical stroke (table 3).

Table 3

Significant carotid stenosis, presence of potential cardioembolic sources and an infarct on CT scan in lacunar and cortical stroke patients

	Lacunar Stroke	**Cortical Stroke**	**(c) OR 95% CI**	**p**
Significant carotid stenosis	22/220‡ (10)	108/358‡ (30)	0.26 (0.16-0.42)	< 0.01
Potential cardiac embolic sources	43/287 (15)	205/582 (35)	0.32 (0.23-0.46)	< 0.01
Infarct on CT scan	187/281# (66)	431/555# (78)	0.57 (0.41-0.79)	< 0.01

‡ patients who had non-invasive carotid test
# patients who had CT scan

The lower frequency of carotid and cardiac sources of embolism in the lacunar stroke patients support the view that lacunar stroke is usually caused by small-vessel disease. Carotid lesions and emboligenic heart disease in the lacunar stroke patients may merely be indicators of generalised atherosclerosis (70,98).

Maastricht Brain Infarct Registry
Registry form

Part I

Stroke date: / /

Registration date: / /

Registration number:

Family name :

Date of birth : / /

Sex ☐ male ☐ female

1. Vascular risk factors

☐ Hypertension
☐ Diabetes mellitus
☐ Ischaemic heart disease
☐ Smoking
☐ Hypercholesterolaemia
☐ Excessive alcohol use
☐ COPD
☐ Peripheral vascular disease

2. Clinical syndrome

☐ Cortical
☐ Unknown
☐ Other .....
☐ Lacunar:
  ☐ PMS
  ☐ SMS
  ☐ PSS
  ☐ AH/DCHS

Affected hemisphere ☐ left ☐ right

3. Bamford Clinical Classification

☐ LACS
☐ TACS
☐ PACS
☐ POCS

4. Rankin Score on admission:

5. Potential cardioembolic sources

- ☐ Atrial fibrillation (paroxysmal, chronic)
- ☐ Recent myocardial infarction (< 6 weeks)
- ☐ Valvular disease or prothesis
- ☐ Cardiomyopathy
- ☐ Left ventricular aneurysm
- ☐ Intraventricular thrombus
- ☐ Other

6. Carotid investigation ☐ no ☐ yes date: / /

1. Duplex* .. right .. left
2. Doppler HTG .. right .. left
3. Angiography .. right .. left

* A = normal
B = 5-15% diameterreduction
C = 26-49% diameterreduction
D1 = 50-79% diameterreduction
D2 = 80-99% diameterreduction
E = occlusion

Please note the most severe degree of internal carotid artery stenosis on both sides

7. Other rare definite stroke causes

- ☐ Vasculitis
- ☐ Carotid dissection
- ☐ Coagulation abnormalities
- ☐ Peri-operative
- ☐ Other

8. Definite Stroke Cause (after CT scan and other ancillary investigations)

- ☐ Small-vessel occlusion
- ☐ Large-vessel atherosclerosis
- ☐ Cardioembolic
- ☐ Other rare definite stroke cause

Part II (CT-scan)

1. CT scan performed ☐ no ☐ yes date: / /

2. Result CT scan ☐ normal ☐ abnormal

number of infarcts: ..

3. Please describe each infarct

1. Hemisphere: ☐ left ☐ right
2. Compatible infarct: ☐ no ☐ yes ☐ uncertain
3. Haemorrhagic: ☐ no ☐ yes

4. Infarct type:

☐ small deep lacunar
☐ striatocapsular
☐ large subcortical
☐ cortical territorial
☐ small centrum semi-ovale
☐ cortical (external) borderzone infarct
☐ internal borderzone
☐ unclassified

5. Infarct size:

1. Small deep-lacunar and internal borderzone infarct :

diameter .. (mm)

and

volume .. (mm^3)

2. Cortical / others

☐	small	(small branch)
☐	moderate	(larger branch)
☐	large	(major artery)

N.B. Striatocapsular and large subcortical: moderate

6. Vascular territory

A. Lacunar	B. Cortical
☐ medial and lateral lenticulostriate artery from MCA ☐ anterior lenticulostriate artery from ACA (Heubner's artery) ☐ anterior choroidal artery from ICA ☐ thalamoperforating artery from PCA	☐ ACA ☐ MCA ☐ PCA

7. Location of infarct

A. Lacunar	B. Cortical
☐ nucleus caudatus ☐ anterior leg anterior CI ☐ anterior leg posterior CI ☐ genu CI ☐ posterior leg anterior CI ☐ posterior leg medial CI ☐ posterior leg posterior CI ☐ thalamus ☐ corpus striatum ☐ corona radiata anterior ☐ corona radiata posterior ☐ combination	☐ frontal ☐ parietal ☐ temporal ☐ occipital According to Bories .....

8. White matter hypodensities (leuko-araiosis)

☐ no
☐ around frontal horn
☐ around occipital horn
☐ sella media

PART III (follow up)

1. Date follow-up: / /

2. Interval follow-up stroke date months

3. Rankin score

4. Recurrent stroke ☐ no ☐ yes

   1. date / /

   2. clinical syndrome (see part 1):
      hemisphere ☐ left ☐ right

   3. CT scan performed ☐ no ☐ yes date: / /

      infarct type (see part II):

   4. Definite stroke cause (see part I):

5. Death ☐ no ☐ yes date: / /

Cause:
☐ Stroke
☐ Cardiac
☐ Other vascular
☐ Non-vascular

Chapter 3

Is Extra-Cerebral Small-Vessel Disease Exclusively Related to Lacunar Stroke Patients with Presumed Cerebral Small-Vessel Disease?

Presented at the European Stroke Conference, Bordeaux, France, June 1-3, 1995

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Submitted for publication

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Abstract

Background. Lacunar infarcts result from a vasculopathy of the small vessels of the brain. It is not known whether this small-vessel disease is exclusively related to the brain or part of a more generalised extra-cerebral small-vessel disease. In this study patients with a lacunar stroke are investigated for manifestations of extra-cerebral small and large-vessel disease in comparison with cortical stroke patients.

Methods. Twenty-nine patients with a lacunar stroke, presumably due to small-vessel disease, and 30 patient with a cortical stroke, presumably due to large-vessel disease, entered the study. Extra-cerebral large-vessel disease was investigated using carotid and renal duplex scanning and Doppler sonography of the major leg vessels. Extra-cerebral small-vessel disease was studied from photographs of the retina, renal perfusion scintigraphy before and after ACE-inhibition, plasma renine measurement, and capillary microscopy of the nailfold. The incidence of hypertension, diabetes mellitus, ischaemic heart disease and hypercholesterolaemia were similar in both groups.

Results. Carotid stenosis (>50%) was significantly less frequent among lacunar stroke patients (lacunar 3% vs cortical 50%, (c)OR = 0.04;95%CI 0.01-0.21, $p<0.01$). Large-vessel disease in the kidney (lacunar 23% vs cortical 27%), and in the legs (lacunar 38% vs cortical 37%) was similar in both groups. There was a high frequency of retinal arteriolosclerosis in both groups (lacunar 92% vs cortical 80%), but predominantly mild. Renal blood flow changes and plasma renin concentrations did not differ between both groups. Both lacunar and cortical stroke patients had normal capillary morphology, red blood cell dynamics were reduced in both subgroups, indicating some degree of small-vessel dysfunction.

Conclusion. Both lacunar and cortical stroke patients have manifestations of extra-cerebral small and large-vessel disease. Therefore, extra-cerebral small-vessel disease is not exclusively related to lacunar stroke patients who presumably have cerebral small-vessel disease.

Introduction

Small and large-vessel disease of the brain are distinctive vascular diseases, which may symptomatically manifest themselves as lacunar and cortical stroke, respectively. Especially the small vessels of the brain cannot be visualized accurately or studied directly during life, whereas small vessels in other parts of the body, such as the retina, nailfold and renal vessels, are more easily accessible for investigations. The occurrence of vascular changes in the retina, nailfold or kidney may provide more information on the nature of the vasculopathy concerning lacunar stroke. However, it is still not known whether cerebral small or large-vessel disease ischaemic stroke patients have their vessel disease restricted to the brain, or suffer from a more generalised vascular disease.

Therefore, incidence and extent of extra-cerebral small and large-vessel disease in patients with lacunar or cortical stroke was investigated.

Patients and Methods

Patient population

From a prospective brain infarct registry (described in chapter 2) at the University Hospital of Maastricht, 60 consecutive patients fitting the study protocol were investigated. All patients had standard stroke investigations, including brain CT scan. Vascular risk factors were noted. Patients with a potential cardiac source of embolism atrial fibrillation (AF), infective endocarditis, cardiomyopathy, cardiac valve disease including prosthetic valve, recent myocardial infarction (<6 weeks), intraventricular thrombus, or paradoxical embolus in the presence of a patent foramen ovale), were excluded because we aimed to study primary cerebral small and large-vessel disease.

The following vascular risk factors were noted and defined as described in chapter 2: hypertension, diabetes mellitus, hypercholesterolaemia, ischaemic heart disease, and smoking.

Ischaemic stroke subtypes were defined as described in chapter 2.

Large vessel investigations

Presence of large-vessel atherosclerosis was investigated in the carotid, renal and major leg arteries by coworkers blinded to the stroke type.
The *carotid* and *renal arteries* were investigated with duplex scanning. Significant large-vessel atherosclerosis of the carotid and renal artery was defined as a stenosis of $\geq$ 50%. The *major leg arteries* were investigated with segmental blood pressure recordings and Doppler ultrasonography. Significant large-vessel atherosclerosis of the leg arteries was diagnosed when the ankle-to-brachial pressure (that is the ratio of the systolic blood pressure at the ankle and the upper arm in supine position) was lower than 95%, and/or when Doppler tracing of the major arteries in the leg showed 1. absence of back flow; 2. diminished pulsatility; 3. prolonged rise-time to peak velocity.

Small-vessel investigations

The presence of small-vessel disease was investigated in the retinal, renal, and nailfold arteriolae performed by co-workers blinded to the stroke type.
The small arteries or *arteriolae of the retina* were studied on photographs by an expert ophthalmologist. The degree of arteriolosclerosis was graded according to the Scheie classification from grade 0 (normal) to grade 4 (severe arteriolosclerosis) (127). The vascular changes were graded on the basis of alteration of the light reflex from the arteriolae and on signs of arteriovenous compression. Slight increase of the light reflex associated with minimal arteriovenous compression was graded as 1, and more prominent changes as grade 2. Presence of copper-wire arterioles and more marked arteriovenous compression determined grade 3, whereas grade 4 with silver-wire arterioles indicated the most severe degree of arteriolosclerosis.

The *renal arteriolae* were investigated indirectly with renal perfusion by nuclear imaging techniques. Renal blood flow (RBF) of each kidney was calculated as described by Peters (118). Briefly, after an intravenous bolus injection of 5mCi Technetium-99-DTPA, first-pass time-activity curves were recorded over the abdominal aorta and both kidneys. Scintillation data were acquired in a supine posterior position for 10 minutes by means of a computer-linked gamma camera. Kidney depth was measured from a lateral image by putting radioactive markers over the abdominal wall. Correction was made for gamma camera sensitivity and background. By scaling the integrated fitted aorta curve, with the upslope parallel to that of the renal curve, and by correction of kidney depth, RBF values can be obtained as a

fraction of the cardiac output. Studies were performed with and without angiotensin-converting enzyme (ACE)-inhibition on successive days. ACE-inhibition was achieved by an oral dose of 50 mg Captopril given 1 hour before the study. Normally, ACE-inhibition results in an increase of the RBF, whereas renal arteriolosclerosis may lead to a diminished increase of the RBF after ACE-inhibition. Furthermore, active plasma renin concentrations were measured by the IRMA method (132). Venous blood samples were taken 1 hour before the first RBF study. Active renin values for normal controls (>50 years) range from 5.6-46.6 mU/L (132). In case of a significant renal artery stenosis, the RBF measurements of the patient in question were excluded from the analysis, because the RBF results could be influenced by a functional stenosis. Plasma renin concentrations in these patients were also excluded for analyses.

The *nailfold* small vessels of the index-finger on the non-affected side were investigated by intravital videomicroscopy. Intravital video capillary microscopy enables assessment of both morphological and haemodynamic parameters of the nutritive part of the skin microcirculation. The experimental set-up has been described in detail before (76). Briefly, a Leitz microscope is equipped with a Ploem-opak and a Pol cube for incident illumination (133). A TV camera (Philips Newvicon XQ 1275, 2/3 inch tube) is positioned in the intermediate plane of the microscope. Images are displayed on a monitor screen (Philips LDH 2122; 12 inch) and stored on videotape by a videocassette recorder (Sony Betamax SL-C9 ES) for off-line analysis, using a flying spot device (144). The following morphologic parameters were measured: 1) Capillary Density (CDe, mm^{-2}), defined as the number of erythrocyte-perfused capillaries per square millimeter of nailfold skin, measured approximately 1.6 mm proximal to the terminal row of capillaries and 2) Capillary Diameter (CDi, in μm), represented by the width of the red blood cell column, measured halfway the arteriolar limb. Also the following haemodynamic parameters were determined: 1) red blood cell velocity under resting conditions (RBCVr, μm/s) and 2) red blood cell velocity at peak of reactive hyperaemia (RBCVp, μm/s). In case of small-vessel disease one would expect either morphological changes (reduced capillary density and/or capillary diameter), or haemodynamic changes (reduced red blood cell velocity under resting conditions or at peak of reactive hyperaemia) in the nailfold.

Measurements were performed following acclimatization in a temperature-controlled room with a temperature between 24°C and 25°C. The subject was sitting in a chair with the hand placed at heart level on the stage of the microscope. After 20 minutes of acclimatization, capillary microscopy was

performed on the nailfold of the index-finger. Relative motion between skin and microscope was prevented by embedding the finger in a mass of clay. Images of capillaries were recorded during one minute. Subsequently, arterial occlusion was induced for one minute, with a cuff around the upper arm. After acute deflation of the cuff, images were recorded during reactive hyperaemia, again during one minute. Capillary morphology and red blood cell velocity were assessed off-line in at least three capillaries. Patients refrained from smoking and did not take caffeine or alcohol at least one hour before examination. To assess possible differences between both stroke subgroups and fully uncompromised extremities, a group of 25 age- and sex-matched healthy volunteers was used as controls.

Statistical analysis

Dichotome variables were analyzed by means of crude odds ratios ((c)OR) with 95% confidence intervals (CI) and χ^2 test, both with Yates' correction. Numeric results per group were characterised by medians and the non-parametric Mann-Whitney U test was used to test for significant differences between both stroke subgroups.

Results

Patients

Results of 59 patients were analyzed. One patient was excluded from the study because of the diagnosis primary intracerebral haemorrhage, which was initially classified as a haemorrhagic infarction. Twenty-nine patients had a lacunar and 30 a cortical stroke. Baseline characteristics including vascular risk factors were similar in both stroke groups (table 1).

Table 1

Baseline characteristics of lacunar and cortical stroke patients

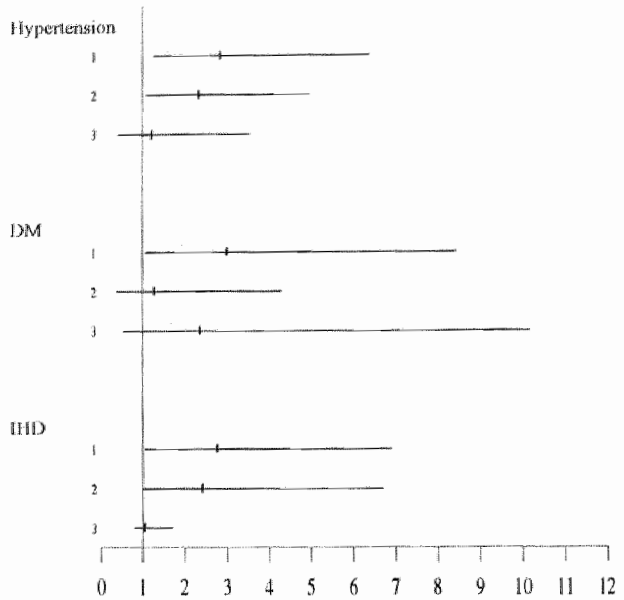
Baseline characteristics	**Lacunar Stroke (N=29)**		**Cortical Stroke (N=30)**		**(c) OR 95% CI**	**P**
	No.	(%)	No.	(%)		
Median age (range) in yrs	65	(50-78)	68	(47-78)		
Male sex	19	(66)	17	(57)	1.61 (0.26-7.98)	NS
Hypertension	11	(38)	10	(33)	1.22 (0.42-3.55)	NS
Diabetes mellitus	6	(21)	3	(10)	2.35 (0.54-10.16)	NS
Ischaemic heart disease	5	(17)	5	(17)	1.04 (0.79-1.73)	NS
Smoking	16	(55)	16	(53)	1.08 (0.32-3.36)	NS
Hypercholesterolaemia	3	(10)	3	(10)	1.44 (0.29-17.4)	NS

An odds ratio (OR) > 1 indicates that the characteristic is more frequent in lacunar stroke patients.

The vascular risk factors hypertension, diabetes mellitus and ischaemic heart disease compared in both stroke subtypes with controls as described in chapter 2, yielded that these risk factors were significantly more often in both stroke groups, with the exception of diabetes mellitus in the cortical stroke patients. Figure 1 shows the comparison of these vascular risk factors in lacunar and cortical stroke patients with the controls.

Figure 1

Comparison vascular risk factors in patients with lacunar or cortical stroke and controls.



Odds ratios with 95% confidence intervals.

1. Lacunar stroke patients vs controls; 2. Cortical stroke patients vs controls; 3. Lacunar stroke patients vs cortical stroke patients.

The incidence of the vascular risk factors in both stroke groups in this chapter were lower than in our entire series of stroke patients as analysed in chapter 2. CT showed a small deep infarct in 21 of the 29 patients (72%) with lacunar stroke and an infarct involving the cortex in 25 of the 30 patients (83%) with cortical stroke.

Large-vessel investigations

Duplex scanning of the renal arteries could not reliably be performed in 3 patients with lacunar and in 8 patients with cortical stroke because the kidney could not be visualized, due to obesity or patient's non-cooperation. Results of the large-vessels investigation are shown in table 2. Large-vessel

atherosclerosis of the carotid artery was significantly less frequent in lacunar stroke patients. Frequency of large-vessel atherosclerosis of the renal and major leg arteries was similar in both stroke subgroups. About 25% of the patients had large-vessel atherosclerosis of the renal arteries, and one third of the patients had atherosclerosis of the major vessels of the legs.

Table 2

Frequency of large-vessel atherosclerosis of the carotid, renal and major leg arteries in lacunar and cortical ischaemic stroke patients

	Lacunar Stroke N=29		**Cortical Stroke N=30**		**(c) OR 95% CI**	**p**
	No.	(%)	No.	(%)		
Carotid artery	1	(3)	15	(50)	0.04 (0.01-0.21)	<0.01
Renal artery	6	(23)#	6	(27)#	0.90 (0.25-3.30)	NS
Major leg arteries	11	(38)	11	(37)	1.06 (0.56-1.98)	NS

An odds ratio (OR) > 1 indicates that the characteristic is more frequent in lacunar stroke patients.

In 3 lacunar and 8 cortical stroke patients renal artery duplex scanning could not be performed reliably.

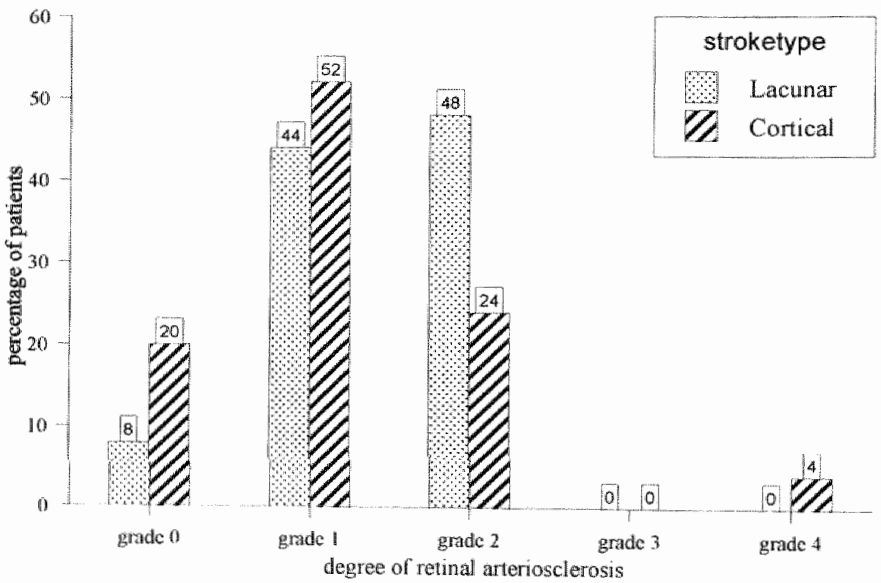
Small-vessel investigations

Retinal arteriolae

Four lacunar and 5 cortical stroke patients were excluded from this part of the study because of cataract, insufficient quality of the retinal photographs, or patient's non-cooperation. The results of the retinal investigations are shown in figure 2.

Figure 2

Distribution of retinal arteriolosclerosis in lacunar and cortical stroke patients.



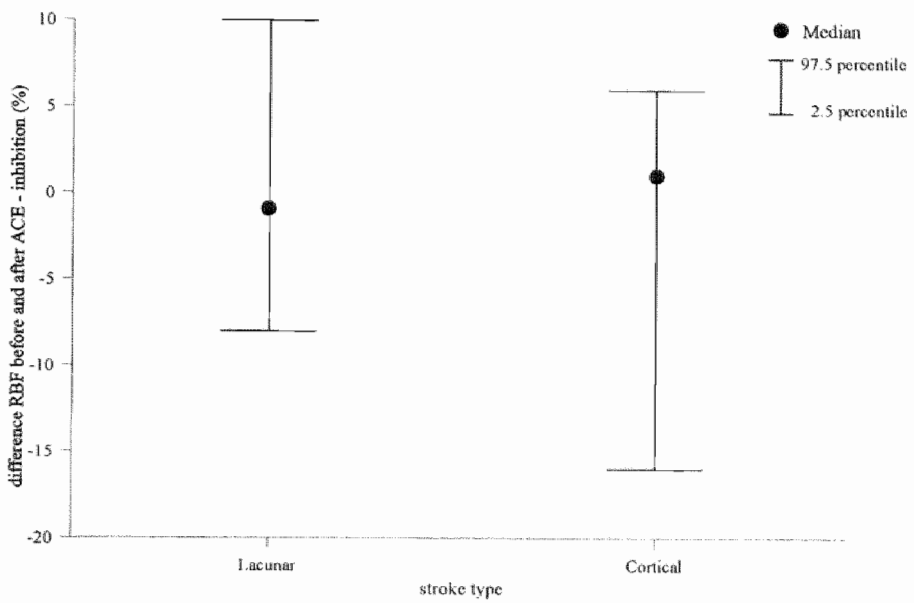
Retinal arteriolosclerosis occurred in 92% of the lacunar stroke patients, and in 80% of the cortical stroke patients, but this difference was not statistically significant ((c)OR 2.88; 95% CI 0.23-36.43). The lacunar stroke patients had a more severe degree of retinal arteriolosclerosis than the cortical stroke patients, but the difference was not statistically significant (χ^2 (for trend) 1.17; p =0.27).

Renal arteriolae

In the analysis of the renal perfusion scintigraphy studies, 9 lacunar and 14 cortical patients were excluded due to significant renal artery stenosis (6 lacunar and 6 cortical stroke patients), inconclusive renal artery duplex scanning (3 lacunar and 7 cortical stroke patients), and refusal of one cortical stroke patient to participate in this part of the study. Therefore, 40 RBF studies in the lacunar and 32 RBF studies in the cortical stroke group were suitable for analysis. The results of the RBF studies before and after ACE-inhibition are shown in figure 3.

Figure 3

Differences of the Renal Blood Flow (RBF) before and after ACE-inhibition, expressed as medians and 97,5 and 2,5 percentile ranges, in lacunar and cortical stroke patients.



There was no significant difference in the changes of RBF after ACE-inhibition between the both stroke groups (p=0.35). Sixteen (40%) lacunar and 12 (38%) cortical stroke patients had a reduced RBF after ACE-inhibition ((c)OR 1.1;95% CI 0.43-2.89), as a sign of renal small-vessel disease. Median active plasma renin concentrations were similar in both groups (lacunar 16.1 mU/l vs cortical 17.6 mU/l;p=0.53). Two patients

(one in each stroke group) had elevated active plasma renin concentrations (lacunar 1 (2.5%) vs cortical 1(3%);(c)OR 0.79: 95%CI 0.36-1.77).

Nailfold capillaries

Three lacunar and 3 cortical stroke patients were excluded from the analysis, because the nailfold capillaries could not be visualized adequately. The results of intravital video capillary microscopy are summarised in table 3.

Table 3

Results obtained with Capillary Microscopy of the nailfold capillaries in the lacunar and cortical stroke patients and in 25 controls (expressed as medians and interquartile ranges)

	Lacunar stroke N=26		Cortical stroke N=27		Controls N=25	
Morphologic parameters						
Capillary density	55	(44-65)	53	(42-65)	51	(43-64)
Capillary diameter	10	(9-11)	10	(9-11)	11	(9-12)
Haemodynamic parameters						
Red blood cell velocity at rest	261	(118-428)	217*	(123-348)	333	(236-472)
Red blood cell velocity at peak of reactive hyperaemia	584**	(450-690)	529***	(291-637)	743	(572-1085)

* $P < 0.05$ (cortical stroke versus controls)
** $P < 0.05$ (lacunar stroke versus controls)
*** $P < 0.01$ (cortical stroke versus controls)

Both capillary density and capillary diameter did not differ between patient groups and controls. As compared to controls, the red blood cell velocity under resting conditions was lower in the cortical stroke patients ($P < 0.05$), whereas the peak red blood cell velocity during reactive hyperaemia was lower in both the cortical ($P < 0.01$) and the lacunar stroke patients ($P < 0.05$). There were no differences between both groups, neither in red blood cell velocity under resting conditions nor in peak red blood cell velocity during reactive hyperaemia.

Discussion

This study shows that both lacunar and cortical stroke patients have manifestations of extra-cerebral large and small-vessel disease. Therefore, extra-cerebral small-vessel disease is not exclusively related to lacunar stroke patients who presumably have cerebral small-vessel disease. The presence of extra-cerebral large-vessel disease in both lacunar and cortical stroke patients probably reflects similar degree of generalised atherosclerosis related to similar vascular risk profiles.

Patients with lacunar stroke may have one of the two pathologically defined small-vessel diseases, microatheromatosis or lipohyalinosis (or arteriolosclerosis), of which microatheromatosis is the most prevalent (11). The nature of microatheromatosis is probable similar to large-vessel atherosclerosis with similar vascular risk factors, whereas only the size of the afflicted vessels differs. This may explain the absence of differences in extra-cerebral vascular manifestations between the lacunar and cortical stroke patients. Our small patient numbers did not allow separate analysis of lacunar stroke patients with small-vessel atherosclerosis or small vessel lipohyalinosis. We therefore cannot exclude the possibility that lacunar stroke due to lipohyalinosis reflects a generalised small-vessel disease subtype (20,103).

About 15% of the patients with lacunar stroke have (pre-)cerebral large-vessel atherosclerosis (21), whereas 15% of the cortical stroke patients have signs of cerebral small-vessel disease reflected by the presence of asymptomatic lacunar infarcts (22). Obviously, a minority of lacunar and cortical stroke patients have signs of both *cerebral* small and large-vessel disease, whereas most of our patients have signs of *extra-cerebral* small and large-vessel disease. From these findings we may conclude that vascular risk factors have a different effect on the carotid arteries and other large vessels, suggesting that other factors such as shear rate stress also play a role.

We were faced in this study with the difficulties of performing a number of different investigations in patients with neurological deficits. Some of the investigations, like photographing the retina, duplex scanning the renal artery and capillary microscopy, could therefore not reliably be performed, especially in patients with more severe deficits. This may have led to bias in the small series we studied, although the number of drop-outs did not differ greatly between both groups.

The degree of generalised vascular disease in our study group may have been less than in the entire stroke population from which these patients were selected. The frequency of several vascular risk factors in our study was lower than compared with the entire stroke group in chapter 2, and consequently they differed less from the controls. However, these differences were similar in lacunar and cortical stroke patients in this study, and therefore a bias towards under or over estimation of these features studied in this chapter in either stroke type is unlikely.

The finding of fewer carotid artery stenosis among lacunar stroke patients is in line with previous studies (17,137), and supports the concept that lacunar infarcts are usually caused by local obstruction of a small perforating artery due to small-vessel disease, rather than embolism.

Large-vessel atherosclerosis of the renal and major leg arteries occurred in about 25 and 40% in both patients groups respectively, reflecting similar atherogenic background in both stroke subtypes (17,21,95). The major leg arteries were investigated with segmental blood pressure recordings and Doppler sonography. This method to investigate the large vessels has proved to be valid and reproducible (57). In the literature, no other data on investigations of the major leg arteries in stroke patients are available. Two previous studies used a history of leg claudication as a marker of large-vessel atherosclerosis in stroke patients. Four percent of the lacunar patients in one study, and 11% in the other study had leg claudication, a frequency that did not differ from cortical stroke patients (95,117).

Non-invasive investigation of the renal arteries with duplex scanning was introduced recently. Renal duplex scanning is a reliable technique for detecting a stenosis of more than 50% (85). However, in up to 15% of patients it is not possible to visualize the renal artery adequately, as was the case in our study. There are no data from the literature available about renal artery disease in stroke patients to compare with our results.

The degree of arteriolosclerosis of the retina was graded with the Scheie classification. This grading system proved to be fairly reliable. In a series of lacunar stroke patients assessed for retinal disturbances according to the Scheie classification, the degree of agreement between two observers corrected for chance, expressed as kappa, was 0.51 (80). We found arteriolosclerosis, which was predominantly mild, of the retinal vessels in most patients in both stroke groups. Three other studies (80,86,126) that investigated the retinal vessels in lacunar stroke patients yielded similar results, they also found high frequencies of mild small-vessel disease in the

retina (80 to 95%). However, these studies only investigated lacunar stroke patients, and the results could therefore not be compared with other stroke subtypes.

Both lacunar and cortical stroke patients had a normal capillary morphology, but the RBCV was reduced in both subgroups, indicating some degree of small-vessel dysfunction. Nailfold capillary microscopy is a valid and reproducible technique investigating the microcirculation (145). Disturbances in the microcirculation using nailfold microscopy have been described in a few diseases, such as lower limb ischaemia, Raynaud phenomena, and reflex symptomatic dystrophy (76,87,145). The only previous study (41) on capillary morphology and lacunar stroke compared 20 lacunar, 20 cortical stroke patients, and 20 healthy controls. In all 3 groups in 25% of the subjects tortuous loops were found, but no loss of capillaries or enlarged loops. In 90% of the 20 lacunar stroke patients in that study, the subpapillar venous plexus was visible, but in only 15% in the two other groups. Despite the other normal morphologic parameters, the authors suggested that the presence of the subpapillar venous plexus in the lacunar stroke patients indicated a generalised small-vessel disease in these patients. However, observing the subpapillar venous plexus only reflects the thickness of the skin, but it has no microcirculatory meaning.

The findings of our study do not support the idea that symptomatic cerebral small or large-vessel disease reflect separate and distinctive generalised small or large-vessel disease. Presence of generalised manifestations of either vasculopathy does not help to ascertain the type of underlying cerebral vasculopathy in symptomatic stroke.

Chapter 4

Haemostatic Parameters Following Lacunar Stroke

This study was supported by a research grant from the Netherlands Heart Foundation.

Abstract

Background. Lacunar and cortical stroke have a distinct pathogenesis with involvement of the cerebral small and large vessels respectively. However, it is still unknown why patients with a similar vascular risk profile may suffer from different stroke subtypes. Haemostatic disorders may be involved.
Methods. We therefore studied various haemostatic parameters in 30 patients with acute cortical stroke and in 29 patients with acute lacunar stroke. Blood samples were obtained within 48 hours after stroke onset and before starting antithrombotic therapy. We measured haematocrit, platelet count, fibrinogen, Antithrombin, protein C activity, activated protein C (APC)-resistance, total and free protein S antigen, Willebrandfactor antigen, lupus anticoagulant (LAC) and anticardiolipin antibodies (ACA). Age, sex and the vascular risk profile were similar in both stroke groups.
Results. Fibrinogen was in the high normal range for both groups compared with the reference range. Mean values of all other haemostatic parameters were normal in both groups. Ten lacunar (34%) and 12 cortical (40%) stroke patients had elevated fibrinogen. Two patients had low ACA IgM antibodies (titers 1/50), one in each group. ACA IgG antibodies were not found, and in none of the patients LAC was detected. Four patients (both in each group) had decreased levels of protein S antigen (range 35-61%, normal > 65%).
Conclusions. There are no differences in haemostatic parameters between cortical and lacunar stroke in the acute phase. Secondly, the equally elevated fibrinogen levels in a substantial number of lacunar and cortical stroke patients support that this might be a risk factor in both stroke subtypes.

Introduction

Several brain infarct subtypes with distinct vascular pathology can be distinguished. Lacunar stroke usually results from small-vessel occlusive disease, whereas the usually cause of cortical stroke is (thrombo)embolism from the (extra)cranial arteries or from the heart. Lacunar and cortical stroke patients do not differ with respect to vascular risk profile (17,21,95), which indicates similar atherogenic conditions. Other, yet unknown factors might therefore be involved in the pathogenesis of the two stroke subtypes.

Haematological abnormalities might contribute to the development of ischaemic stroke in the presence of vascular pathology (66,104).
Primary haematological disorders are the cause of ischaemic stroke in approximately 1% of all strokes, and up to 4% in young stroke patients (66). These include qualitative and quantitative disorders of the platelets and erythrocytes, and a number of acquired and hereditary forms of hypercoagulability (thrombophilia) such as deficiencies of coagulation inhibitors (antithrombin, protein C and protein S), antiphospholipid antibodies, homocysteinaemia and impaired fibrinolysis. Recently a new hereditary disorder of blood coagulation has been described, the so-called activated protein C (APC) resistance, which appeared to be due to a mutation in coagulation factor V (factor V Leiden) (10,34,134). An association between APC resistance and ischaemic stroke, especially in young adults, was recently suggested (64,93,131).

Few studies (40,56,84,135,136,152) compared haemostasis in lacunar and cortical stroke by measuring activation markers of haemostasis, such as fibrinopeptide A and D-dimer. The results of these studies are controversial, but tend to indicate that the degree of haemostatic activation is higher in patients with cortical stroke. More haemostatic parameters were measured in the study of Kilpatrick (84), but the small number of patients in this study does not allow to draw firm conclusions.

In this study we investigated haemostatic parameters in lacunar stroke patients in comparison with cortical stroke patients in order to determine whether haematological disorders are involved in the pathogenesis of lacunar stroke.

Patients and Methods

From the prospective brain infarct registry at the University Hospital of Maastricht (as described in chapter 2), 59 patients fitting the study protocol, were investigated. All patients had standard investigations including brain CT scan. Vascular risk factors such as hypertension, diabetes mellitus, history of ischaemic heart disease, smoking and hypercholesterolaemia, were defined as described in chapter 2. Patients with cardioembolic infarction were excluded because we aimed to study haemostatic differences between brain infarcts presumably due to cerebral small-vessel and large-vessel disease.

Lacunar stroke, resulting from presumed small-vessel disease, and cortical stroke, resulting from presumed large-vessel disease, were defined according to the definitions previously described in chapter 2. Fifty-nine patients were investigated, of whom 29 had lacunar and 30 had cortical stroke. Baseline characteristics are shown in table 1 of chapter 3. The cortical stroke patients had more frequently a significant carotid stenosis, whereas there were no other significant differences between both groups.

Blood samples were taken within 48 hours after stroke onset and before starting antithrombotic therapy. Venous blood was collected by vena puncture from the non-affected arm, between 9.00 and 10.00 A.M. in fasting state. The co-worker who performed and assessed the laboratory tests was blind to the stroke type of the patients. We measured platelet count, fibrinogen (Clauss method), antithrombin (coamatic antithrombin, Kabi, Sweden), protein C activity (coamatic protein C, Kabi, Sweden), activated protein C (APC)-resistance (coatest APC resistance, Kabi, Sweden), total and free protein S antigen (rabbit immunoglobulins to human protein S, Dako, Denmark), v. Willebrand factor antigen (rabbit immunoglobulins, Dako, Denmark), lupus anticoagulant (LAC) screening with RVVT (Russel's viper snake venom, Sigma, U.S.A), Factor 2 antigen (rabbit immunoglobulins, CLB, the Netherlands) and anticardiolipin antibodies (ACA) (goat F(ab)2-conjugate, Cappel Organon, AKZO, U.S.A). ACA antibodies titers were present above the lower limit of detection (1/50).

Results are presented per stroke subgroup. Haemostatic parameters were compared with normal reference ranges used in our hospital. These values were derived from 55 healthy controls (38 male and 17 women, median age 38, range 25-53 years). Dichotome variables were analyzed by means of crude odds ratios ((c)OR) with 95% confidence intervals and χ^2 test, both with Yates' correction. For numeric variables, means and standard errors are

given. Differences in haemostatic parameters were assessed using the Wilcoxon rank-sum test.

Results

Table 1 summarises the results of the haemostatic tests. Mean values of all haemostatic parameters were normal for both groups; fibrinogen, however, was in the high normal range for both groups compared with the reference range. Four patients (2 in each group) had decreased levels of free protein S antigen (range 35-61%, normal > 65%). Ten lacunar and 12 cortical stroke patients had elevated plasma fibrinogen (lacunar 34% vs cortical 40%: (c)OR 0.79;95%, CI 0.05-12.27). Two patients had low ACA IgM antibodies (titers 1/50), one in each group. ACA IgG antibodies and LAC were not detected.

Table 1

Haemostatic parameters in patients with acute lacunar or cortical ischaemic stroke

	Lacunar stroke (N=29)	Cortical stroke (N=30)	Range of Normal Values
Platelet count, 10^9/l	216 ± 57	237 ± 84	130-350
Antithrombin activity, %	98.1 ± 11.7	100 ± 7.9	80-120
Prot.C activity, %	110 ± 19.2	99.9 ± 28.8	65-130
APC ratio	3.4 ± 0.4	3.2 ± 0.7	>2.5
Tot. Prot.S antigen, %	112 ± 14	104.3 ± 24.7	65-130
Free Prot.S antigen, %	87.3 ± 26.9	81.7 ± 37.6	65-130
v WF antigen, %	137.5 ± 29.9	136.1 ± 35.3	50-200
RVVT, seconds	23.9 ± 0.4	23.7 ± 0.9	22-25
Factor 2 antigen, %	113 ± 19	111 ± 23	60-140
Fibrinogen, g/l	4.1 ± 1.1	4.0 ± 1.0	1.7-4.0

Results are expressed as the mean ± 1 SD for both stroke subtypes

Discussion

This study shows no differences in haemostatic parameters between lacunar and cortical stroke in the acute phase following stroke.

We found low free protein S levels, which is in agreement with the findings of others (60,104,123). One prior study compared protein S levels between lacunar and cortical stroke and, like us, found no difference (104). Low levels of free protein S are not only found in cerebral ischaemia, but have also been demonstrated in hospitalised control subjects, even in the absence of a recognised predisposing condition (104). Presumably, the majority of low levels of free protein S are acquired and appeared usually to be transient. Because protein S forms an inactive complex with C4b-binding protein, which is an acute phase reactant, acquired free protein S may result from a decrease in the ratio of free protein S to bound protein S (33).

In 1 lacunar and 1 cortical stroke patient we found low titers of ACA IgM antibodies. Low titer ACA IgM are a finding of doubtful significance and transiently positive tests for ACA IgM, such as occurring in infections, may be of less meaning (62). In none of our patients LAC was detected. The association between antiphospholipid antibodies and stroke is controversial. Most studies favouring the association (72,88,92,110,115), studied selected series (especially young adults), failed to include age-matched controls and failed to adjust for co-existing disorders known to predispose to stroke (112). Reported prevalence of raised ACA titers among stroke patients and healthy elderly varies widely range from 0 to 21%, and 0 to 50%, respectively (28,102,143). A recent case-control study showed no evidence to support the hypothesis that ACA is an independent risk factor for ischaemic stroke (112). The only significant difference between patients and controls in this study was found for IgG ACA in the oldest patient group (72-96 years) with a single vascular risk factor. It was concluded that IgG ACA is probably an epiphenomenon in patients with atherosclerotic vascular disease rather than a causative agent. An other case control study (138) demonstrated that ACA was an independent risk factor for stroke. However, only 2 of 24 positive patients were without any vascular risk factor (112). Kilpatrick et al. (84) found LAC in 3 of 9 patients with lacunar stroke, and in 1 cortical stroke patient. They suggested a possible role for LAC in lacunar stroke despite the small number of patients.

In none of our patients APC-resistance was found. This hereditary disorder with an autosomal dominant trait which is due to a mutation in blood coagulation factor V, predominantly manifest itself with venous thromboembolism and rarely with arterial thrombosis (10). Recently, a few case-reports in young patients suggested an association between APC-resistance and ischaemic stroke (64,93,131). Therefore, case-control studies to asses the true association between APC-resistance and ischaemic stroke are proposed (131).

We found high normal fibrinogen levels in both stroke subgroups, whereas fibrinogen was elevated in a substantial number of lacunar and cortical stroke patients. The marked elevations of fibrinogen may partly be attributed to the higher age of the patients than the controls. However, epidemiological and clinical studies have demonstrated an association between elevated levels of plasma fibrinogen and ischaemic stroke (77,130,150). The relation between plasma fibrinogen and increased risk for vascular diseases was also demonstrated in coronary artery disease. A meta-analysis of 6 prospective studies and the recently published ECAT study identified fibrinogen as an independent risk factor (39,140). Although elevated fibrinogen formation could be relevant to the stroke cause, it may also be caused by nonspecific release of procoagulants from damaged cerebral tissue (40,139). It remains unclear whether elevated fibrinogen levels are a reflection of a preexisting prethrombotic state, possible in synergy with other vascular risk factors, or merely a secondary phenomenon occurring as a consequence of cerebral parenchyme necrosis. Support for a possible causal role of fibrinogen in these stroke subtypes could be the finding of a persistent elevation in subsequent months after the stroke.

The findings in this study suggest that it is unlikely that haemostatic abnormalities play an important role in the pathogenesis of lacunar and cortical stroke. Secondly, the equally elevated fibrinogen levels in a substantial number of lacunar and cortical stroke patients support that this is a risk factor in both stroke subtypes.

Chapter 5

Lacunar Stroke is Associated with Human Leukocyte Antigen HLA-B35

Boiten J, Luijckx GJ, Van den Berg-Loonen E, Lodder J. Lacunar stroke is associated with Human Leukocyte Antigen HLA-B35.

Submitted for publication

This study was supported by a research grant from the Netherlands Heart Foundation.

Abstract

Background. Patients with lacunar or cortical stroke have a similar vascular risk profile. What determines whether the small or large vessels will become affected in the presence of the same atherogenic circumstances, remains unknown. A genetic predisposition may be involved.

Methods. We determined the Human Leukocyte Antigen (HLA) frequencies in 59 consecutive patients with lacunar or cortical stroke, who were registered in the prospective brain infarct registry at the University Hospital of Maastricht.

Results The 29 lacunar stroke patients had a significantly higher incidence of HLA-B35 compared to 295 controls (41% vs 18%; (c)OR = 3.15, 95% CI 1.37-7.24, $p<0.05$) and 30 cortical stroke patients (41% vs 13%; (c)OR = 4.59, 95% CI 1.13-18.65, $p<0.05$). No significant differences were found for all other HLA class I and class II antigens.

Conclusions. Our findings demonstrate an association between lacunar stroke and HLA-B35, which suggests a genetic predisposition for developing this distinct type of ischaemic stroke resulting from cerebral small-vessel disease.

Introduction

Symptomatic cerebral small-vessel and large-vessel disease have distinct stroke syndromes and different prognosis, and require different stroke management (7,8,65,81). These two types of cerebral vasculopathies can be visualized on computed tomography (CT) or magnetic resonance imaging (MRI) as small deep, so-called lacunar, infarcts or as large, cortical (superficial) infarcts, respectively.

Clinical studies have shown a similar vascular risk profile in patients with lacunar or cortical stroke (17,21,96). What determines whether the small vessels or large vessels will become affected in the presence of the same atherogenic circumstances, remains unknown. A genetic predisposition to develop either small-vessel or large-vessel disease may be involved. Some diseases are associated with particular Human Leukocyte Antigens (HLA), which means that the genetic inheritance of a particular HLA antigen gives an individual an altered risk of developing a particular disease (141).
We determined the HLA frequencies in patients with lacunar or cortical stroke to investigate a possible genetic predisposition for either of these two stroke entities.

Patients and methods

From the prospective brain infarct registry at the University Hospital of Maastricht, as described in chapter 2, 59 consecutive patients fitting the study protocol, were investigated. All patients had standard investigations including brain CT scan. Vascular risk factors (hypertension, diabetes mellitus, history of ischaemic heart disease, hypercholesterolaemia and smoking), and significant carotid stenosis were defined as in chapter 2. Patients with cardioembolic infarction were excluded because we aimed to study brain infarcts presumably due to cerebral small-vessel and large-vessel disease. Lacunar stroke resulting from presumed small-vessel disease and cortical stroke resulting from presumed large-vessel disease were defined as in chapter 2. Fifty-nine Caucasian patients were investigated, of whom 29 had lacunar and 30 cortical stroke. The baseline characteristics are shown in table 1 of chapter 3. There were no other significant differences between both groups in baseline characteristics, except that the cortical stroke patients had more frequently a significant carotid artery stenosis.

Serological HLA typing was performed by standard microcytotoxicity assays for both class I and class II antigens. Class I typing was routinely carried out

for 21 A-, 50 B- and 10 C-locus antigens. Class II typing detected DR1 through 18, DR51-53 and DQ1 through 9. The co-worker who performed HLA typing was blind to the stroke syndrome of the patient. The results of both groups were compared with a control group of 295 healthy Caucasians. The presence of a particular HLA type is independent from age and sex, in contrast to race. Patients and controls were all of the Caucasian race.

Differences between the groups were analysed by means of odds ratios ((c)OR) with 95% confidence intervals (CI) and χ^2 test, both with Yates' correction.

Results

Lacunar stroke patients had a significantly higher incidence of HLA-B35 compared to controls (12 of 29 patients (41%) vs 54 of 295 controls (18%); OR = 3.15, 95% CI 1.37-7.24; χ^2 = 7,3, $p<0.05$), and cortical stroke patients (12 of 29 patients (41%) vs 4 of 30 patients (13%); OR = 4.59, 95% CI 1.13-18.65; χ^2 = 4,54, $p<0.05$), whereas incidence was similar in cortical stroke patients and controls (4 of 30 patients (13%) vs 54 of 295 controls (18%); OR = 0.69, 95% CI 0.12-3.85; χ^2 = 0.18, $p>0.5$). A higher incidence was also noted for Cw4 due to linkage disequilibrium with B35. No significant differences were observed for all other HLA class I and class II antigens. The calculated risk (so-called relative risk) of an individual carrying HLA-B35 to develop lacunar stroke due to small-vessel disease compared to someone not carrying HLA-B35 is 3,3.

Discussion

We found an association between lacunar stroke and the HLA-B35 antigen, which suggests that a genetic predisposition for developing lacunar stroke resulting from cerebral small-vessel disease may be involved. A genetic predisposition may explain the development of cerebral small-vessel disease in the presence of similar vascular risk factor profiles that cause large-vessel disease. Clarification of how HLA-B35 relates to the development of cerebral small-vessel disease may ultimately provide opportunities for prevention of this stroke entity.

Hypertension and diabetes mellitus account only partially for the risk of lacunar stroke (21). Therefore, genetic factors involved in these risk factors (24) do not explain this possible genetic predisposition for developing lacunar stroke.

Recently, findings on a rare genetic stroke syndrome involving the small vessels of the brain were reported (23). This disease has been called CADASIL: an acronym for Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (23). CADASIL has an autosomal dominant pattern of inheritance, and the disease locus has been assigned to chromosome 19q12 in two unrelated French families (142). The patients had recurrent subcortical (lacunar) strokes, whereas MRI showed small, deep (lacunar) infarcts and white matter lesions (leukoencephalopathy) (23). Neuropathological examination demonstrated multiple small, deep (lacunar) infarcts with atrophy and diffuse pallor of the hemispheric white matter (9). The underlying small-vessel vasculopathy is different from arteriosclerotic and amyloid angiopathies (9), but has similarities with small-vessel lipohyalinosis (or arteriolosclerosis) as described in patients with hypertension and multiple lacunar infarcts (46,50). In CADASIL and lipohyalinosis, the whole vessel wall is involved, with destruction through deposits in the media, with the smallest vessels being mainly involved. However, in contrast to lipohyalinosis, the nature of the deposits in CADASIL is unknown (9). At present 25 families with CADASIL have been identified, demonstrating that this disorder is probably not as rare as originally thought of (23). Although we did not investigate family members, our patients did not fit the severity of clinical and neuroradiological features and progression as described in the CADASIL patients. Therefore, we believe that the relationship between HLA-B35 and lacunar stroke in our patients is unlikely to be due to CADASIL. However, further studies have to clarify this issue.

As we hypothesized (20) and as recently confirmed by others (103), the existence of two clinically distinct lacunar subtypes, further studies may yield a subgroup which is stronger associated with HLA-B35. Probably these two clinically distinct subtypes reflect the two types of small-vessel vasculopathy, microatheromatous disease and lipohyalinosis in lacunar stroke (20). In line with CADASIL, which underlying vasculopathy has similarities with lipohyalinosis, patients with multiple lacunar infarcts, who probably have lipohyalinosis, may have a stronger association with HLA-B35 than the patients with a single symptomatic lacunar infarct who probably have microatheromatous disease.

Chapter 6

Small-Vessel Disease Is the Single Likely Cause of Lacunar Stroke Among Young Patients

Adapted from:

Gert-Jan Luijckx, Jelis Boiten, Jan Lodder, Lisette Heuts-van Raak, Fons Kessels. Cardiac and carotid embolism, and other rare definite disorders are unlikely causes of lacunar ischaemic stroke in young patients.

Cerebrovascular Diseases; in press

Abstract

Background. The difference in brain infarct causes between younger and elderly stroke patients may largely depend on differences in the cause of cortical infarcts, the pathogenesis in small deep (lacunar) infarcts being more homogeneous. To test this hypothesis, we studied infarct subtypes related to the cause in young in comparison with elderly stroke patients.
Methods. We therefore compared clinical features, vascular risk factors and stroke causes between 60 brain infarct patients of 50 years or less and 756 patients older than 50 years, in relation to the stroke subtype. As stroke causes were considered: small-vessel disease, atherothrombosis or large vessel disease, cardioembolism and other rare definite causes, such as cervical artery dissection, vasculitis, coagulation disorders, surgery related disorders etc.
Results. Bivariate analysis showed that other rare definite infarct causes were significantly more frequent among young stroke patients (15% vs 3%, ((c) OR = 6.2; 95% CI 2.8-13.6). All these young patients had a cortical stroke. The whole group of lacunar stroke patients (young and old) had significant less frequently rare definite stroke causes than the whole group of cortical stroke patients (1% vs 5%, (c)OR 0.22; 95% CI 0.07-0.71).
Conclusion. Young patients have a more varying cause of brain infarction than older patients, but this is largely confined to those with a cortical stroke. Our data suggest that other rare definite disorders, and cardiac or carotid embolism are unlikely stroke causes in young patients with a lacunar stroke.

Introduction

Distinction between lacunar (small deep) and cortical (superficial) stroke is important because their pathogenesis and prognosis differ (17,46,50,95). Lacunar strokes are usually caused by small-vessel disease with local obstruction of a small perforating artery (46,50), whereas cortical strokes are caused by large-vessel atherosclerosis or by embolism from the heart. The cause of an ischaemic stroke is not only related to the stroke subtype, but also to the patient's age. Younger patients in general have a relatively high frequency of rare stroke causes unlike elderly patients, in whom atherosclerosis is by far the most common cause (2,11,14,67,79).

The view that lacunar strokes usually result from local small-vessel obstruction is still under discussion (12,90,108). If rare definite stroke causes would largely be confined to cortical stroke in both young and elderly patients, one would expect the underlying vascular pathology in lacunar stroke to be independent of age. To test this hypothesis, we studied the relationship between ischaemic stroke subtype and stroke cause in young patients, in comparison with elderly patients. If in most young patients lacunar stroke is caused by small-vessel occlusion, a different approach to diagnostic investigations in such patients might result.

Patients and methods

Patient population

The patients come from a prospective registry at the University Hospital of Maastricht of all patients with a first-ever episode of supratentorial brain ischemia with symptoms lasting longer than 24 hours as described in chapter 2. Patients aged 50 years or less were called "young" and those aged over 50 years were called "old" or "elderly". All patients had standard stroke investigations. Vascular risk factors (hypertension, diabetes mellitus, history of ischaemic heart disease), and significant carotid stenosis (diameter reduction >50%), were defined as in chapter 2. Echocardiography, 24 hours ECG monitoring and cerebral angiography were performed in selected cases, also depending on the age of the patient. Young patients more often had extensive cardiac examination including (transesophageal) echocardiography and cerebral angiography whereas older patients more often had 24 hours ECG monitoring.

Definitions

Ischaemic stroke subtypes:
Lacunar stroke and *cortical stroke* are defined in chapter 2.

Ischaemic stroke causes:
Small-vessel occlusion, large vessel atherosclerosis, cardioembolism and rare definite stroke causes are defined in chapter 2.

Statistical analysis
Differences between two groups were analyzed in a bivariate analysis by means of crude odds ratios ((c)OR) with 95% confidence intervals (CI), and χ^2 test, both with Yates' correction. Multivariate logistic regression analysis was performed to determine the association of age, sex, hypertension, diabetes mellitus, a history of ischaemic heart disease, significant ipsilateral carotid stenosis, cardioembolic source or the presence of another rare definite stroke cause, with the ischaemic stroke subtypes (lacunar or cortical) as dependent variable; for statistical analysis adjusted odds ratios ((a)OR) with 95% CI were determined. The association between stroke subtype and rare definite stroke causes may differ between the younger and older age group. Therefore, to determine whether age was an effect modifier, an interaction term was added to the multivariate logistic model. Because of our a priori hypothesis that the association between a rare definite stroke cause and cortical stroke is stronger in young patients, one-tailed testing determined the significance level.

Results

816 patients were registered with a first supratentorial brain infarction of whom 269 (33%) had a lacunar infarct and 547 (67%) a cortical infarct. Sixty patients (7%) were 50 years or younger. Of the 269 patients with a lacunar stroke 23 were young (9%), whereas of the 547 patients with a cortical stroke 37 were young (7%). All 60 young patients had a CT scan, which showed a compatible infarct in 51 (85%). Of the 756 old patients 721 (95%) had a CT scan; 560 (78%) had a compatible infarct on CT.

Demographic characteristics, vascular risk factors and stroke causes in the two age groups and stratified for the two stroke subtypes are shown in table 1.

Table 1

Demographic characteristics, vascular risk factors, and stroke causes in 816 ischaemic stroke patients stratified for age group and stroke subtype

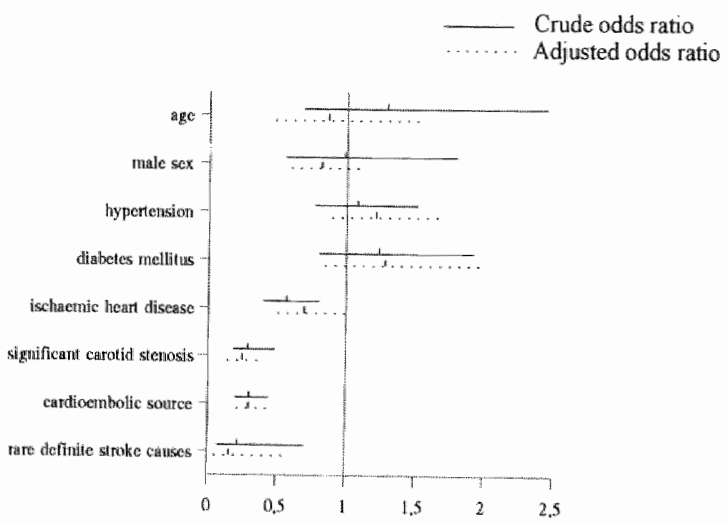
Baseline characteristics	Patients ≤ 50 years N = 60				Patients >50 years N = 756			
	Lacunar stroke N=23 (38%)		Cortical stroke N=37 (62%)		Lacunar stroke N=246 (33%)		Cortical stroke N=510 (67%)	
	N	(%)	N	(%)	N	(%)	N	(%)
Demographic features								
mean age	44		41		70		73	
male sex	13	(57)	19	(51)	136	(55)	285	(56)
Vascular risk factors								
hypertension	10	(43)	11	(30)	118	(48)	239	(47)
diabetes mellitus	2	(9)	3	(8)	44	(18)	75	(15)
ischaemic heart disease	3	(13)	3	(8)	50	(20)	162	(32)
significant carotid stenosis	1	(4)	7	(19)	27	(11)	142	(28)
cardioembolic source	1	(4)	10	(27)	35	(14)	176	(35)
Stroke causes								
small-vessel occlusion	23	(100)	-		243	(99)	-	
large-vessel atherosclerosis	-		18	(49)	-		316	(62)
cardioembolism	-		10	(27)	-		176	(34)
rare definite stroke causes	-		9	(24)	3	(1)	18	(4)

The vascular risk factor profile was similar for the two age groups, except for ischaemic heart disease, which occurred significantly less often in the younger age group (10% vs 28%;(c)OR:0.29; 95% CI 0.12- 0.67; $p<0.01$). Rare definite stroke causes were more frequent among the young patients (15% vs 3%;(c)OR 6.2; 95% CI 2.8-13.7; $p<0.001$). Remarkably, all these rare definite stroke causes among the young patients were found in those with a cortical stroke. Of the 21 old patients who had a rare definite stroke cause, 18 had a cortical and 3 a lacunar stroke. Of the 9 young patients with a rare definite stroke cause, 5 had a spontaneous carotid artery dissection, 2 causes were surgery related, 1 had a vasculitis, and 1 had a hypercoagulable state. In the 21 older patients, 9 strokes were surgery related (of which 8 to cardiac surgery), 3 occurred during systemic hypotension, and 2 during hypertensive crisis, 4 occurred during or after angiography (2 carotid and 2 coronary angiography), 2 by vasculitis, and 1 by hypercoagulable state. Figure 1 compares demographic, vascular risk factors, and stroke causes (except for small-vessel occlusion and large-vessel atherosclerosis, which, by

definition, are only present in one stroke subtype), between lacunar and cortical stroke by bivariate (expressed as (c)OR with 95% CI) and multivariate logistic regression analysis (expressed as (a)OR with 95% CI). Patients with lacunar stroke had significantly less frequent a significant carotid stenosis, a potential cardioembolic source, and rare definite stroke causes. Addition of an interaction term between age and a rare definite stroke cause resulted in an almost significantly better fit of the model ($p=0.06$)

Figure 1

Comparison between lacunar and cortical stroke by bivariate and multiple logistic regression analysis. An OR < 1 indicates that the variable is less strongly associated with lacunar stroke.



Odds ratio with 95% Confidence Intervals

Angiography in search for rare vascular disorders, e.g. extracranial artery dissection or vasculitis, was more often abnormal in young than in old patients (17% vs 3%;(c)OR 6.2;95% CI 1.1-36.9;$p<0.05$). All 6 young patients with angiographic abnormalities (5 with carotid artery dissection and 1 with a vasculitis) had a cortical stroke, whereas the angiograms performed in 19 of the 23 patients with a lacunar stroke were normal. Among the 62 elderly who had angiography, a rare definite vascular disorder was shown in

only 2 patients (both with vasculitis), of which one had a cortical and the other a lacunar stroke.

Discussion

We found that rare definite stroke causes were approximately 5 times less frequent in lacunar than in cortical stroke patients. Remarkably, among young patients these causes were confined to those with a cortical stroke, whereas none of the young lacunar stroke patients had a rare definite stroke cause. In our logistic regression model, age modified the effect of rare definite stroke causes on stroke subtype, in that the association between rare definite stroke causes and cortical stroke was stronger in young patients. As in lacunar stroke patients in general (17,95), potential cardiac or carotid sources of embolism were less frequent in young lacunar stroke patients than in young cortical stroke patients. Therefore, our findings suggest that lacunar stroke in young patients may have a similar cause as in elderly patients, which is most likely local small-vessel occlusion in most cases. Proof of this could only come from pathological studies which, however, are unlikely to be performed because of the low early case fatality rate of lacunar stroke patients.

In several studies on stroke in young patients the upper age limit was chosen arbitrarily between 45 and 50 years. We choose an age limit of 50 years mainly because of a former collaborative study (101). All our young patients with a rare definite stroke cause were younger than 45. Therefore, a different age limit would not have affected our results essentially, but confidence intervals would have been wider.

In the diagnostic work-up of young stroke patients angiography is regarded as mandatory in those patients in whom otherwise a rare definite stroke cause cannot be diagnosed or excluded with certainty (2). In some of our young patients with a cortical stroke, but in none with a lacunar stroke, angiography revealed a rare definite stroke cause. Therefore, our data question the need of angiography in search of rare vascular disorders in all young lacunar stroke patients, but this suggestion may need confirmation by larger series.

Chapter 7

Topography of Isolated Hemiataxia in Lacunar Stroke

Adapted from:

Gert-Jan Luijckx, Jelis Boiten, Jan Lodder, Lisette Heuts-van Raak, Jan Wilmink. Isolated hemiataxia following supratentorial brain infarction.

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Abstract

Background. Acute isolated hemiataxia is in most cases due to infratentorial (cerebellar) stroke, whereas it has only been described twice in supratentorial stroke, namely following thalamic infarction and a capsular haemorrhage.
Methods. Patients who presented with isolated hemiataxia were selected from the Maastricht Brain Infarct Registry. Clinical features and CT and/or MRI findings were studied.
Results. Three patients with isolated hemiataxia following a supratentorial brain infarct were found. These patients were seen in a period of almost 6 years during which 899 patients with a first supratentorial brain infarct were registered. Clinically the hemiataxia was of the cerebellar type. CT and MRI showed in two patients a small, deep (lacunar) infarct restricted to the posterior limb of the internal capsule, a site not previously reported in isolated hemiataxia. The third patient had a small, deep (lacunar) infarct in the thalamus extending into the adjacent posterior limb of the internal capsule.
Conclusions. Isolated hemiataxia following a supratentorial brain infarct is a very rare clinical stroke syndrome. The cerebellar-type hemiataxia was most likely caused by interruption of the cerebellar pathways at the level of the internal capsule. Our cases confirm prior observations that the cerebellar pathways run through the posterior part of the posterior limb of the internal capsule separately from the motor and sensory pathways.

Introduction

Hemiataxia following a supratentorial brain infarct is not uncommon. However, in most cases hemiataxia is accompanied by either ipsilateral motor (ataxic hemiparesis) or sensory signs (hemiataxia-hypaesthesia), or both (hypaesthetic ataxic hemiparesis), whereas it rarely occurs in isolation. Isolated hemiataxia following supratentorial brain infarction has only once been described in thalamic infarction and following a small haemorrhage in the internal capsule (52,100). We now report on 3 patients with isolated hemiataxia following a supratentorial brain infarct. Two of these patients had a small, deep (lacunar) capsular infarct, a site not reported before in isolated hemiataxia.

Patients and Methods

The patients were selected from the Maastricht Brain Infarct Registry, which is a prospective registry at the University Hospital of Maastricht of all patients with a first-ever supratentorial brain infarct with symptoms lasting longer than 24 hours, as described in chapter 2. All patients had either cranial computed tomography (CT) or magnetic resonance imaging (MRI), or both. Routine investigations included: standard blood and urine tests, non-invasive carotid studies and an electrocardiogram. Presence of vascular risk factors, carotid stenosis, and cardioembolic sources as described in chapter 2 were recorded.

The patients were followed prospectively every 3-6 months. We selected those patients who presented with hemiataxia, being defined as a unilateral incoordination on finger-to-finger, finger-to-nose and heel-to-shin tests with dysmetria, hypermetria, intention tremor, or dysdiadochokinesia or combinations of these signs.

Results

899 patients were registered with a first-ever supratentorial brain infarct. Of these, 47 patients (5,2%; 95% CI 4.9-5.5%) had hemiataxia, which in 43 patients was accompanied by either motor or sensory signs, or both. Four of these 47 patients had isolated hemiataxia, in 3 of whom brain imaging showed a symptomatic lesion. Clinical features of these 3 patients together

with CT and MRI findings are described in more detail in the following case reports:

case 1:
A 63-year-old man, known with a history of hypertension and smoking, suddenly developed clumsiness of the left arm and unsteadiness of gait without weakness. On admission the same day neurologic examination showed left-sided dysmetria, hypermetria and intention tremor on finger-to-finger, finger-to-nose and heel-to-shin tests. Somatosensory evoked potentials were normal. CT on day 4 showed a hypodense lesion in the posterior limb of the right internal capsule, compatible with a small, deep (lacunar) infarct. MRI after 3 months showed the same lesion (figure 1 panel A and B). Neurologic examination after 6 weeks was normal. Also at a follow visit after 6 months no abnormalities were found on neurological examination.

case 2:
A 65-year-old woman with a history of ischemic heart disease and atrial fibrillation, suddenly experienced clumsiness of the right hand with unsteadiness of gait without weakness. The symptoms had a stuttering onset, and were progressive during 48 hours. Neurologic examination on day 3 showed right-sided dysmetria, hypermetria and intention tremor on coordination tests. Somatosensory evoked potentials were normal. Incoordination was more prominent in the arm than in the leg. CT on day 9 demonstrated a small, hypodense lesion in the posterior limb of the left internal capsule compatible with a small, deep (lacunar) infarct (figure 1 panel C). Ataxia improved during the next 3 months. After 3 months the patient suddenly died of myocardial infarction. Autopsy was not obtained.

case 3:
A 68-year-old man with a history of hypercholesterolaemia, complained of transient dysarthria, persisting sudden clumsiness of the right arm and unsteadiness of gait without weakness. Neurologic examination on the same day showed right-sided dysmetria and hypermetria on finger-to-finger, finger-to-nose and heel-to-shin tests, and dysdiadochokinesia. Ataxia of the arm was more severe than that of the leg. Somatosensory evoked potentials were normal. CT on day 8 showed a small, hypodense lesion in the left lateral thalamus extending into the adjacent posterior limb of the internal capsule compatible with a recent infarct. Ataxia improved during the following 6 weeks , at which time the neurologic examination showed only slight ataxia on finger-to-finger and finger-to-nose tests. MRI, which was made 4 months later after the patient had had a recurrent cortical stroke in the same hemisphere, showed the same thalamocapsular lesion (figure 1 panel D).

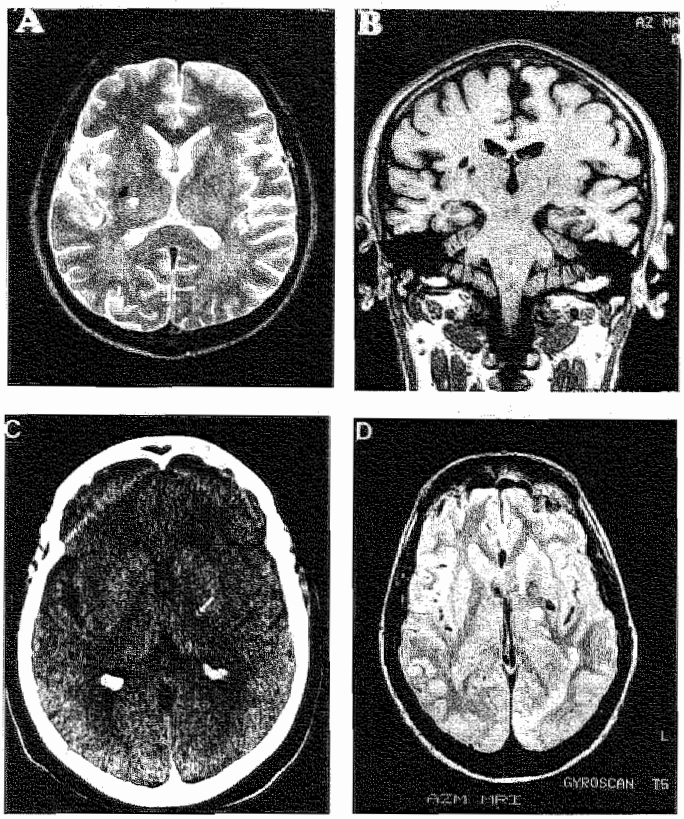

Figure 1:

Panel A: Transverse MRI, T2 weighted, of patient 1 showing a small deep lesion with high signal intensity in the posterior limb of the internal capsule on the right side (arrow).

Panel B: Coronal T1 weighted MRI showing the same lesion in the posterior limb of the right internal capsule (arrow). The lesion does not involve the thalamus.

Panel C: Transverse CT section of patient 2 showing a small hypodense ischemic lesion in the posterior limb of the internal capsule on the left side (arrow).

Panel D: Transverse proton density weighted MRI of patient 3 showing a lesion with high signal intensity in the left lateral thalamus extending into the adjacent posterior limb of the internal capsule (arrow). Also demonstrated are two minute adjacent satellite lesions. Note the cortical infarct in the territory of the left posterior cerebral artery which the patient had experienced four months later, before this MRI was made.

Discussion

Although acute isolated cerebellar ataxia is usually caused by cerebellar stroke our study shows that acute cerebellar hemiataxia may exceptionally be caused by a supratentorially located stroke. Our 3 patients with isolated hemiataxia and a symptomatic, supratentorially located ischemic brain lesion were seen in a period of almost 6 years during which 899 patients were included in our brain infarct registry of all consecutive patients with a first supratentorial brain infarct. Obviously, isolated hemiataxia following a supratentorial stroke is a very rare clinical syndrome.

In previously reported series, hemiataxia following supratentorial brain lesions never occurred in isolation but was accompanied by either motor or sensory signs, or both (68,105,106). Isolated hemiataxia following supratentorial brain lesions has only been reported twice: Fisher described isolated hemiataxia following thalamic infarction (52), whereas we recently reported on isolated hemiataxia caused by a small capsular haemorrhage (100).

Cases of ataxic hemiparesis, in which the cerebellar-type ataxia is associated with ipsilateral motor weakness, are far more common than isolated hemiataxia cases. One could imagine that our patients also had hemiparesis at onset which had already disappeared at the time of examination. However, this seems unlikely because, firstly, 2 of our patients were examined within a few hours after onset; and secondly, in the third patient (case 2) the neurological symptoms were progressive during the first 48 hours after which the patient was examined showing only hemiataxia. In 2 of our patients ataxia was more prominent in the upper than in the lower limb. In none of our patients it was more prominent in the lower limb. The hemiataxia was relatively mild with good resolvement in all 3 cases.

Two of our patients had a small, deep (lacunar) infarct in the posterior limb of the internal capsule. Coronal and transverse MRI sections in one patient clearly showed that the lesion was restricted to the posterior limb of the internal capsule, whereas it did not involve the thalamus. Cases of isolated hemiataxia following a small, deep (lacunar) infarct restricted to the posterior limb of the internal capsule have not been reported before. Our third patient had an infarct of the lateral thalamus extending into the adjacent posterior limb of the internal capsule.

Hemiataxia in our patients was clinically of the cerebellar type. Disturbed propriocepsis as the cause of the ataxia was unlikely because there was no deep sensory loss on clinical testing, whereas eyelid closure did not worsen the ataxia. Moreover, the somatosensory evoked potentials to investigate the proprioception were normal. In ataxic hemiparesis the explanation for ataxia is still controversial. Some authors hypothesised that proprioceptive deficits, e.g. resulting from damage to the ventral posterior nucleus of the thalamus, causes ataxia (111), whereas others ascribed the ataxia to interruption of the cerebellar pathways, e.g. at the level of the internal capsule (75). We considered hemiataxia in our patients to be of the cerebellar type. Therefore, it was most likely caused by damage to the cerebellar pathways, either the ascending dentatorubrothalamocortical pathway or the descending cortico-pontocerebellar pathway at the level of the internal capsule. The two patients with small, deep infarcts in the posterior limb of the internal capsule confirm our prior observations that the cerebellar pathways run through the posterior part of the posterior limb of the internal capsule separately from the motor and sensory pathways (18,100).

Chapter 8

Normal Median Nerve Somatosensory Evoked Potentials Support the Clinical Notion that Hemiataxia After Lacunar Stroke is Cerebellar

Adapted from:

G.J. Luijckx, F. Spaans, J. Boiten, J. Lodder.
Normal median nerve somatosensory evoked potentials support the clinical notion that hemiataxia after lacunar stroke is cerebellar.

Submitted for publication

Abstract

Background. Both cerebellar and sensory dysfunction have been described as the cause of the ataxia in patients with ataxic hemiparesis. In order to determine the cause of the ataxia, we investigated the sensory modalities and performed median nerve somatosensory potentials (SEP) in patients with hemiataxia following lacunar stroke.

Methods. All patients had clinical sensory testing, median nerve SEP studies, and CT or MRI of the brain. SEP results were reviewed for correlation with clinical features and infarct location and size.

Results. Nineteen patients were studied. Twelve patients had ataxic hemiparesis, 4 patients had ataxic hemiparesis with sensory deficits (hypaesthetic ataxic hemiparesis) and 3 had isolated hemiataxia. Fifteen patients had a lacunar infarct on CT or MRI. Eyelid closure did not worsen the ataxia in any of the patients. There was no difference between the mean latency of the SEP components from the affected and non-affected hemisphere. Only 3 of the 19 patients had an abnormal SEP. There was no correlation between SEP findings, clinical features and location or size of the infarcts.

Conclusions. Our findings of a normal SEP in most patients indicate that disturbed proprioception as the cause of ataxia is unlikely and therefore supports the clinical notion that the ataxia is cerebellar. Cerebellar-like ataxia is most likely caused by disruption of the cerebellar pathways at the level of the internal capsule or corona radiata, either the ascending dentatorubrothalamocortical or the descending corticopontocerebellar pathways.

Introduction

Ataxia may result from cerebellar dysfunction (cerebellar ataxia), or from disturbed proprioception (sensory ataxia). Fisher described ataxia in the lacunar syndrome of ataxic hemiparesis as "cerebellar-like" (48,54). In an earlier series of ataxia following lacunar stroke (15,18,100), we suggested that ataxia was unlikely to be caused by disturbed proprioception, because we found normal proprioceptive sensory modalities on clinical testing, whereas eyelid closure did not worsen the ataxia. However, others suggested disturbed proprioception to be the cause of ataxia in ataxic hemiparesis (68,83,111), among others sustained by abnormal somatosensory evoked potentials (SEP). The SEP studies in lacunar stroke comprised only 15 patients with the lacunar syndrome of ataxia hemiparesis (1,5,83,89,111), and only 2 studies dealt exclusively with ataxia and SEP (83,111). Therefore, we studied a consecutive series of patients with ataxia following lacunar infarcts with clinical sensory testing and SEP to determine the cause of ataxia.

Patients and Methods

Patients:
The patients were part of an ongoing registry at the Maastricht University Hospital of all patients with a first-ever supratentorial ischaemic stroke with symptoms and/or signs lasting longer than 24 hours, as described in chapter 2. Routine investigations included standard blood and urine tests, electrocardiography (ECG), chest radiography and noninvasive carotid studies. All patients had cranial computed tomography (CT) or magnetic resonance imaging (MRI).

For this study we selected patients who presented with hemiataxia resulting from lacunar stroke. Hemiataxia was diagnosed as unilateral incoordination on finger-to-finger, finger-to-nose and heel-to-shin tests, with dysmetria, hypermetria, intention tremor, dysdiadochokinesia or combinations of these signs. The following sensory modalities were tested: exteroceptive sensation by light touch and pain, and proprioceptive sensation by position and vibration sense. We distinguished hemiataxia with ipsilateral motor signs (ataxic hemiparesis), ipsilateral sensory signs (hemiataxia-hypaesthesia), ipsilateral motor and sensory signs (hypaesthetic ataxic hemiparesis), and isolated hemiataxia. Lacunar stroke was defined as described in chapter 2. Infarct volume was estimated according to Nelson (114).

Somatosensory evoked potentials:
Median nerve SEP were recorded in 19 patients and in 21 healthy control subjects matched for age and sex. The subjects were examined in a quiet semi-darkened room and no sedative drugs were used. Electrode placements were in accordance with the 10-20 international system at F3, F4, C3, C4, P3, P4 and Cz. An additional electrode was placed over the cervical spine just above C7. Linked ears served as a reference. The stimulation electrode was placed over the median nerve at the wrist with the cathode 3 cm proximal to the anode. The median nerve was stimulated with a pulse duration of 0.2 ms, a rate of 3.7 per second, and an intensity which elicited a modest twitch of the abductor pollicis brevis muscle. Five hundred responses were summated on each run. In each study the left and right median nerve were stimulated separately. The studies were repeated to evaluate the consistency of the recorded responses. Afterwards the two runs were averaged for both sides separately. The averaged response was stored and displayed for measurement.

For analysis of the SEP, we first looked at the presence of NI and NII frontal (F), central (C) and parietal (P), secondly at the latency difference of the peaks between both hemispheres, and thirdly at the amplitude difference of the peaks between both hemispheres. The frontal NI and NII were absent in 7 of the 21 controls and are therefore not included in the analysis. Using the method of Yamada (151), the normal upper limit of the latency difference between both hemispheres was calculated as the mean plus three standard deviations. In the control group the upper limit of the latency difference between both hemispheres was 3.1 msec for C NI, 4.5 msec for C NII, 2.2 msec for P NI and 4.8 msec for P NII. Based on these results from the controls, an abnormal median nerve SEP was defined as follows: 1. absence of C NI, C NII, P NI or P NII; 2. prolonged latency difference of C NI, C NII, P NI or P NII between both hemispheres; 3. an amplitude difference of more than 50% between both hemispheres.

Results

Clinical findings
Nineteen patients with hemiataxia following lacunar stroke had a median nerve SEP study. There were 12 men (63%) and 7 women (37%) with a median age of 70 (range: 52-83) years. Twelve patients had the clinical syndrome of ataxic hemiparesis, 4 patients had hypaesthetic ataxic hemiparesis, and 3 had isolated hemiataxia. In all patients eyelid closure did not worsen the ataxia. CT or MRI revealed in 15 patients a small deep

(lacunar) infarct, of which 5 were located in the posterior limb of the internal capsule, 3 in the posterior part of the corona radiata, 3 in the lentiform nucleus, 2 thalamocapsular, 1 in the thalamus and 1 in the anterior part of the corona radiata. Eight infarcts were located in the anterior choroidal artery territory, 4 infarcts in the lenticulostriate arteries territory, and 3 in the thalamoperforating arteries territory. Volumes of the infarcts ranged from 0.18 ml to 2.45 ml, median 0.59 ml.

Median nerve SEP findings

SEP studies were performed 5 days (median; range 2-9) after onset of the neurologic deficit. Table 1 shows the mean latency of the peaks evoked by stimulation of the median nerve contralateral to the affected hemisphere in comparison to the non-affected hemisphere for all patients. There were no differences in the latencies between the hemispheres for central and parietal NI and NII .

Table 1

Mean latency $\pm$ S.D. (in msec) of the central and parietal NI and NII of the median nerve SEP after stimulation contralateral to the affected and to the non-affected hemisphere in the 19 patients studied. The numbers of patients in whom peaks could be identified are placed between parentheses.

	Peaks	Affected hemisphere	Non-affected hemisphere
NI	Central	20.0 $\pm$ 1.4 (18)	19.8 $\pm$ 1.7 (19)
	Parietal	20.4 $\pm$ 1.9 (18)	20.5 $\pm$ 1.6 (19)
NII	Central	31.9 $\pm$ 2.9 (16)	32.3 $\pm$ 3.5 (19)
	Parietal	32.5 $\pm$ 3.1 (17)	33.6 $\pm$ 3.3 (19)

Table 2 shows the SEP findings, the clinical syndromes and location of the infarcts for all patients. Only 3 of the 19 patients (16%) had an abnormal SEP. Two of these patients with an abnormal SEP had also hemisensory deficits. In patient #1 the sensory modalities light touch, pain, position and vibration sense were disturbed. In this patient no cortical SEP was obtained from the affected hemisphere. The other patient (#15) had paraesthesias in the arm and leg. Two other patients (#9,10) with hemisensory deficits (both diminished light touch sense, but with normal propriocepsis) had normal SEP. All patients with abnormal SEP had mild motor deficits as well (MRC

scale muscle power degree 4) (38). Two patients with an abnormal SEP had an infarct on CT. One was located in the lentiform nucleus (patient #1) and the other in the posterior part of the corona radiata (patient #12). The presence of an abnormal SEP was not related to the infarct volume (Mann-Whitney U test: $p=0.12$).

Table 2

Clinical syndrome, location of the infarct, and SEP findings in 19 patients with hemiataxia following a lacunar ischaemic stroke.

No	Clinical syndrome	Infarct location	SEP abnormalities
1.	HAH	LN	all cortical responses absent in the affected hemisphere
2.	AH	CRA	-
3.	AH	ICPL	-
4.	AH	-	-
5.	AH	-	-
6.	AH	ICPL	-
7.	AH	LN	-
8.	AH	CRP	-
9.	HAH	Th-C	-
10.	HAH	ICPL	-
11.	AH	-	-
12.	AH	CRP	NII C and P absent
13.	AH	LN	-
14.	AH	Th	-
15.	HAH	-	ampl. red. > 50%; NII C absent
16.	AH	CRP	-
17.	IH	ICPL	-
18.	IH	Th-C	-
19.	IH	ICPL	-

Clinical syndromes: AH=ataxic hemiparesis; HAH=hypaesthetic ataxic hemiparesis; IH=isolated hemiataxia.

Infarct location: CRA=corona radiata anterior part; CRP=corona radiata posterior part; ICPL=internal capsule posterior limb; LN=lentiform nucleus; Th-C=thalamo-capsular; Th=thalamus.

Discussion

We found that most of our patients with hemiataxia following lacunar stroke had normal median nerve SEP. SEP reflect the integrity of the proprioceptive sensory system (30,31). The normal SEP indicate that disturbed proprioception as the cause of the ataxia is unlikely and therefore supports the opinion based on clinical findings that the ataxia is due to disruption of cerebellar projections.

Few studies looked at median nerve SEP in patients with hemiataxia following lacunar stroke (1,5,83,89,111), and information is available in only 15 patients in total. Most of these patients (10 of the 15) had an abnormal SEP, which is in contrast with our findings. However, the small series of patients reported may have resulted from selective sampling. The consecutive patients in our series were selected from a prospective stroke registry by clinical stroke syndrome. SEP abnormalities did not differ between the several studies and this study, and consisted of latency or amplitude differences of the peaks between hemispheres or absence of peaks in the affected hemisphere.

Several studies on lacunar stroke suggested that only patients with a large infarct or those with accompanying motor signs had abnormal SEP (109,120), whereas others suggested that an abnormal SEP was only related to the location and not to the volume of the infarct (1). Our study was restricted to one lacunar syndrome, whereas the other studies included patients with other lacunar syndromes, particularly pure motor, pure sensory, and sensorimotor stroke, but in our 3 patients with abnormal SEP there was no relationship between SEP abnormalities, clinical signs, and size or location of the infarct.

Disruption of the cerebellar pathways, either the ascending dentatorubrothalamocortical or the descending corticopontocerebellar pathways could explain cerebellar-like ataxia. The infarcts in the posterior limb of the internal capsule, and those in the posterior and anterior part of the corona radiata could have injured either ascending or descending cerebellar pathways, or both. In patients with thalamic involvement, ataxia may be caused by disruption of the dentatorubrothalamocortical pathway, involving the ventrolateral thalamus nucleus (15,25). Involvement of the lentiform nucleus less easily explains the ataxia because the cerebellar pathways do not run through these area. Possibly, initial edema around the infarct compressed and injured the adjacent cerebellar pathways in the internal capsule. Another explanation could be that the visible infarct was not

the symptomatic one, whereas the true symptomatic infarct was not (yet) visible on brain imaging, although the radiological age was also taken into account when considering an infarct symptomatic or not.

We conclude that our SEP findings support the clinical opinion that ataxia following lacunar stroke is of cerebellar type.

General Discussion

Distinction of different ischaemic stroke subtypes is relevant because of consequent differences in patient management. Insight into pathophysiological mechanisms of stroke subtypes may facilitate tailored therapeutical decisions. Lacunar stroke represents a brain infarct subtype that is numerically important; approximately 25% of all first-ever brain infarcts are of the lacunar type. It has distinctive clinical features, and the pathophysiology differs from that in brain infarcts involving the cortex. Generally, lacunar infarcts can reliably be predicted from the signs and symptoms, which are often referred to as "lacunar syndromes". However, less clear is the nature of the underlying pathophysiology. Clinical studies suggest that carotid or cardiac embolism are unlikely causes of lacunar infarcts. Most, that is approximately 90%, of the lacunar infarcts are caused by local obstruction of one of the perforating, small, deep arteries. The size of the infarcts agrees with the idea that occlusion of just one penetrator or one of its branches suffices to result in a lacunar infarct. Pathological proof for the underlying type of small-vessel vasculopathy in lacunar infarction is scarce, which is mainly due to the very low early case fatality rate. The few cases studied at autopsy may, therefore, not be representative for lacunar stroke patients who survived. Based on a few pathological studies Fisher distinguished two types of small-vessel disease in lacunar stroke: microatheromatosis and lipohyalinosis, the first being most common and related to symptomatic lacunar infarcts, whereas lipohyalinosis is less prevalent, and related to asymptomatic lacunar infarcts.

Although the cause of most brain infarcts is atherosclerosis-related, there is potentially a host of diseases that can result in ischaemic stroke. This applies to brain infarcts in general, but it is unknown whether the often called "rare" disorders equally cause lacunar and cortical infarcts. If such "rare" causes would not be found among lacunar stroke patients, this would strengthen the

idea of a distinctive, small-vessel vasculopathy underlying lacunar infarcts. The results described in this thesis indeed strongly suggest that cerebral small-vessel disease is distinctive in the sense that it could only be related to known vascular risk factors and not to other "rare" stroke causes.

The next question is whether such small-vessel disease manifests itself in the brain only or is part of a generalised "distinctive" small-vessel affliction. This thesis shows that signs of small or large-vessel disease in different organ systems are equally present among patients with lacunar or cortical infarction. Apparently, symptomatic cerebral small-vessel disease is not part of a distinctive generalised small-vessel affliction. Moreover, similar degrees of large and small-vessel abnormalities may point at similar atherogenic conditions, as was also suggested earlier from clinical studies comparing vascular risk profiles among lacunar and cortical stroke patients. One may conclude that the cerebral vascular tree differs from that of other organs as to the effects of the known vascular risk factors. What causes either small or large-vessel disease to become symptomatic under certain atherogenic conditions remains unclear. Differences in vascular structure may be involved; cerebral vessels have a thinner adventitia than systemic vessels. Moreover, the cerebral vessels are situated in a peri-vascular space, named after Virchow and Robin, and have a different innervation pattern.

Genetic factors may also be involved. In chapter 4 we found that lacunar and cortical stroke patients differ in HLA-typing, lacunar stroke being associated with HLA-B35 antigen. A recent study also suggested a genetically determined difference between lacunar and cortical stroke patients, as indicated by a difference in the frequency of a deletion polymorphism of the ACE gene. Further studies on genetically determined differences between different stroke subtypes seem promising.

So far, small-vessel disease was discussed as a distinct vascular entity, but the affliction may be less homogeneous. As mentioned above, on pathological grounds at least two types could be distinguished, small-vessel atheromatosis and lipohyalinosis. Clinical studies suggest that these two types may broadly be distinguished during life. Not merely hypertension, but more likely the duration and degree of hypertension may be related to the development of small-vessel lipohyalinosis. Future studies on cerebral small-vessel disease are required to improve our understanding of these two different small-vessel vasculopathies.

The result of the studies described in this thesis strengthen the idea that cerebral small-vessel disease underlying symptomatic lacunar infarcts is a

distinctive vasculopathy. Two subtypes may be distinguished, even during life.

Where to go from here?

What is the clinical significance of the findings in this thesis for patient management, especially when related to the management of acute stroke? Currently, two lines of investigation on the acute treatment of stroke look promising. One aims at early reperfusion of occluded intracranial arteries, and the other at protection of neurons from ischaemia-induced metabolic injury. Both therapeutical options are related to the concept of the so-called ischaemic penumbra, which is a zone of cerebral tissue adjacent to the central core of tissue necrosis. Within the penumbra cell function is severely impaired, whereas without treatment cell death may ensue. Such secondary neuronal death is related to ischemia induced massive release of excitatory neurotransmitters into the cellular interstitium, of which the most important is glutamate. Excitatory amino-acids may activate the so-called NMDA receptor, allowing massive influx of calcium into the cell. Increased cellular calcium content activates different proteolytic enzyme systems resulting in the breakdown of various cellular elements, as a consequence of which cell death may follow. Blocking the NMDA receptor to inhibit cellular calcium influx is currently under investigation in several clinical trials. Such cytoprotective measurements may likely be without any effect in the absence of tissue reperfusion.

Sometimes after cerebral infarction spontaneous reperfusion occurs, especially in the case of embolic stroke. There are no specific features on the basis of which embolic stroke can be distinguished from local thrombosis, but in the presence of a potential cardiac embolic source embolism is likely. However, the timing of reperfusion in cardioembolic stroke cases may vary considerably, whereas there is no clinical evidence that cardioembolic stroke results in less neurological deficits than brain infarcts caused otherwise. Therefore, early reperfusion of the blocked cerebral artery by anti-thrombotics or thrombolytics is currently under investigation. So far a clear benefit of reperfusion therapy has not been demonstrated. A large trial on early anticoagulation is still continuing, whereas several trials on thrombolysis were terminated because of a high number of haemorrhagic complications in the treated groups. A better selection of patients however, may reduce the number of haemorrhagic complications. In this respect, the underlying brain infarct cause as well as the infarct size may be important factors. Furthermore, angiography in the acute phase may demonstrate the

occlusion in the artery or on the other hand spontaneous reperfusion in which case reperfusion treatment is no longer needed.

Lacunar infarcts are unlikely to benefit from thrombolytic therapy because such infarcts are of small size, whereas the degree of clinical deficit is related to the strategical location of the infarct rather than its size. Moreover, the infarct mechanism in lacunar infarcts is not embolic, but due to local small-artery obstruction. Moreover, reperfusion in lacunar infarcts could theoretically more easily lead to cerebral bleeding because of the relatively high arterial pressure in the deep perforator arterial system. In previous thrombolytic studies the presence of small deep infarcts indeed increased the risk of cerebral haemorrhages. Early identification of an infarct as either cortical or lacunar is therefore of utmost importance.

The data from this thesis indicate that no generalised features can predict whether a cerebral infarct is caused by either small or large-vessel disease. Modern sophisticated imaging techniques such as diffusion weighted MRI and SPECT may in the near future be helpful to distinguish different infarct subtypes in the acute phase. But as long as these techniques have not been validated clinically we have to rely on the clinical prediction whether an infarct is lacunar or cortical. Several studies demonstrated that such a prediction can reliably be made, although not always. Transcranial Doppler may be helpful in the diagnosis of intracerebral large-artery disease, but further validation of this technique is indicated. Transcranial Doppler or MRI angiography may replace conventional angiography to demonstrate the occluded artery and to evaluate the results of reperfusion therapy.

The data of this thesis also show that younger lacunar stroke patients should be investigated and treated in a similar way as elderly lacunar stroke patients. Thrombolytic therapy should therefore not be performed in such patients.

What has been said in relation to thrombolysis also holds true for early cytoprotective therapies. Without spontaneous or induced reperfusion cytoprotection is likely to be without effect. It could well turn out in the future that a stroke subgroup benefits from the combination of these therapeutical options.

The term "stroke" is not a uniform diagnosis, neither is "brain infarction". The underlying pathophysiology of a brain infarct may determine patient outcome in clinical trials and dictate future therapy. Therefore, further validation of different brain infarct entities remains important. Although

modern imaging techniques may facilitate the distinction between different brain infarct subtypes, clinical features remain the mainstay upon which the eventual diagnosis is based in most patients. Results reported in this thesis may be helpful in making such distinction.

Summary

The aim of this thesis has been to describe some pathogenetical and clinical aspects of lacunar brain infarction.

In **chapter 1**, after some general remarks on lacunar stroke, the relevant literature on some pathogenetical and clinical aspects of lacunar brain infarction is reviewed. Lacunar brain infarction results from the occlusion of a single, deep perforating, artery. It is not known whether this small-vessel vasculopathy is limited to the brain or whether it is part of a more generalised extra-cerebral small-vessel disease. Investigations of the extra-cerebral small-vessels, as in the retina, kidney and nailfold, which are more easily accessible for investigations than cerebral small vessels, may give more information on the nature of the cerebral small-vessel vasculopathy underlying lacunar stroke. Clinical studies demonstrated that the vascular risk profile in lacunar and cortical stroke is similar. What causes either stroke type under the same atherogenic conditions still remains unknown. Haemostatic abnormalities or a genetic predisposition may play a role in the pathogenesis of lacunar stroke. Ischaemic stroke below the age of 50 is more common than expected. However, the causes are more diverse. It is not known whether these diverse causes are confined to one stroke subtype. Hemiataxia is one of the signs which may occur after lacunar infarction. Isolated hemiataxia following supratentorial lacunar infarction is very rare. Clinical-topographical aspects of isolated hemiataxia need further description. Both cerebellar and sensory dysfunction, on the basis of clinical sensory study and somatosensory evoked potentials (SEP), have been described as the cause of ataxia following lacunar infarction.

In **chapter 2** a description of the Maastricht Brain Infarct Registry (MBIR) is given. Patients were selected from this registry. In the study period from June 1987 to February 1994, 899 patients were registered, 460 men (51%),

and 439 women (49%), with a median age of 71 (range 15 to 96.). 287 patients (32%) had a lacunar stroke, and 582 (65%) patients a cortical stroke. A subgroup with "other rare definite causes" comprised 30 patients (3%). Vascular risk factors for cerebrovascular disease were compared in the entire stroke group, lacunar and cortical stroke group and controls without symptomatic stroke. The frequency of the vascular risk factors was in the entire stroke patients significantly higher than in the controls. The vascular risk profile in lacunar and cortical stroke was similar. However, the frequency of carotid and cardiac sources of embolism was significantly lower in lacunar stroke patients. This finding is in line with the view that lacunar stroke results from cerebral small-vessel disease.

In **chapter 3**, manifestations of extra-cerebral large and small-vessel disease were compared in 29 lacunar stroke patients and 30 cortical stroke patients, with the aim to determine whether extra-cerebral small-vessel disease is exclusively related to lacunar stroke patients. Extra-cerebral large-vessel disease was investigated using duplex scanning of the carotid and renal artery and Doppler sonography of the major leg vessels. Extra-cerebral small-vessel disease was studied from the photographs of the retinal arteriolae, renal perfusion scintigraphy, plasma renin measurements, and capillary microscopy of the nailfold. Apart from carotid artery stenosis, which occurred significantly less frequent among lacunar stroke patients, there were no significant differences in the incidence of extra-cerebral large and small-vessel disease in lacunar and cortical stroke patients. Therefore, extra-cerebral small-vessel disease is not exclusively related to lacunar stroke patients.

In **chapter 4** we studied haemostatic parameters during the acute phase in both lacunar and cortical stroke patients to determine a possible role haematological disorders in the pathogenesis of lacunar stroke. The following haematological parameters were studied: platelet count, fibrinogen, antithrombin, protein C activity, activated protein C (APC) resistance, total and free protein S antigen, v Willebrand factor antigen, lupus anticoagulant, and cardiolipin antibodies. There were no differences in haemostatic parameters between lacunar and cortical stroke in the acute phase following stroke. Fibrinogen was in the high normal range for both stroke subtypes. It is unlikely that haematological abnormalities play an important role in the pathogenesis of lacunar and cortical stroke. The equal levels of fibrinogen support the presence of a similar vascular risk profile in both stroke subtypes.

Chapter 5 describes HLA typing in lacunar stroke patients in comparison with cortical stroke patients, in order to investigate a possible genetic predisposition. The lacunar stroke patients had a significantly higher incidence of HLA-B35 antigen compared with cortical stroke patients and healthy controls. No significant differences were found for all other HLA class I and II antigens. This finding demonstrates an association between lacunar stroke and HLA-B35, which suggests a genetic predisposition for developing this distinct type of stroke resulting from small-vessel disease. The genetic predisposition may explain the development of cerebral small-vessel disease in the presence of similar vascular risk factors that causes large-vessel disease.

In **chapter 6**, we investigated the differences in stroke causes between young and elderly patients with lacunar or cortical stroke. Rare causes, such as carotid dissection, were significantly more frequent among young stroke patients. All these patients had cortical stroke. The whole group of lacunar stroke patients had significantly less frequent a rare cause than the whole group of cortical stroke patients. Young patients had more diverse stroke causes than older patients, but this was confined to the cortical stroke patients. Carotid artery stenosis and cardioembolic sources were, in both young and elderly lacunar stroke patients, significantly less frequent than in cortical stroke patients. These findings support the concept that lacunar infarcts are the result of a cerebral small-vessel disease, irrespective of age. The need for some specific investigations in young lacunar stroke patients, like angiography, can therefore be questioned.

Chapter 7 gives a description of 3 patients with the rare finding of isolated hemiataxia following lacunar brain infarction. Clinical findings argued in favor of a cerebellar type of hemiataxia. CT and/or MRI in 2 patients showed a lacunar infarct in the posterior limb of the internal capsule, whereas the third patient had a thalamo-capsular infarct. Isolated hemiataxia caused by a capsular infarction has never been reported before. The cerebellar-like ataxia is most likely caused by interruption of the cerebellar pathways at the level of the internal capsule, either the ascending dentatorubrothalamocortical or the descending corticopontocerebellar. The fact that hemiataxia was an isolated finding in these patients, demonstrates that the cerebellar pathways at the level of the internal capsule run separately from the motor and sensory pathways.

In **chapter 8**, we studied in a consecutive series of 19 patients with ataxia following a lacunar infarct, the cause of the ataxia with clinical sensory testing and median nerve SEP. All patients had CT and/or MRI of the brain,

and SEP results were reviewed for correlation with clinical features and infarct location and size. In all patients there were no signs of a disturbed proprioception on clinical testing and most median nerve SEP were normal. Most infarcts were located in the posterior limb of the internal capsule or corona radiata. There was no correlation between SEP findings, clinical features and infarct location or size. These findings suggest that disturbed proprioception as the cause of ataxia is unlikely. Interruption of the cerebellar pathways, at the level of the internal capsule or corona radiata is the most likely cause of ataxia following lacunar brain infarction.

Samenvatting

In dit proefschrift worden enkele pathogenetische en klinische aspecten van lacunaire herseninfarcten beschreven.
In **hoofdstuk 1** wordt, na enkele algemene opmerkingen over lacunaire infarcten, een overzicht gegeven van de relevante literatuur over de pathogenetische en klinische aspecten van lacunaire herseninfarcten die werden onderzocht. Lacunaire infarcten worden veroorzaakt door een afsluiting van één der kleine perforerende hersenarteriën, als gevolg van een aandoening van deze kleine perforerende hersenarteriën. Het is niet bekend of deze aandoening van de kleine arteriën beperkt is tot de hersenen of dat deze een onderdeel vormt van een meer gegeneraliseerde aandoening van de kleine arteriën. Kleine arteriën buiten de hersenen, zoals in de retina, nier en het nagelbed, zijn gemakkelijker te onderzoeken dan in de hersenen. Onderzoek van de kleine arteriën buiten de hersenen kan mogelijk meer informatie opleveren over de aard van de onderliggende vaataandoening bij lacunaire infarcten. Klinisch onderzoek heeft aangetoond dat het vasculaire risicoprofiel in lacunaire en corticale herseninfarcten gelijk is. Wat de oorzaak is van ieder afzonderlijk type herseninfarct onder dezelfde atherogene omstandigheden is nog steeds onbekend. Afwijkingen in de hemostase of een genetische predispositie spelen mogelijk een rol in de pathogenese van lacunaire infarcten. Herseninfarcten bij patiënten jonger dan 50 jaar treden vaker op dan men verwacht. Het is echter zo dat de oorzaken van herseninfarcten op jonge leeftijd diverser zijn. Het is onbekend of deze diverse oorzaken beperkt blijven tot één type herseninfarct. Ataxie kan het gevolg zijn van een lacunair infarct. Geïsoleerde hemiataxie ten gevolge van een lacunair infarct is bijzonder zeldzaam. Over de klinisch-topografische aspecten van geïsoleerde hemiataxia is niet veel bekend. Over de oorzaak van de ataxie als gevolg van een lacunair infarct zijn de meningen verdeeld. Zowel een cerebellaire functiestoornis als afwijkingen in de propriocepsis worden als oorzaak beschreven. Dit laatste op basis van klinisch

sensibiliteitsonderzoek en neurofysiologisch onderzoek met somatosensorische evoked potentials (SEP).

In **hoofdstuk 2** volgt een beschrijving van de Maastrichtse Herseninfarct Registratie. De patiënten werden betrokken uit deze registratie. In de studieperiode juni 1987 tot februari 1994 werden 899 patiënten met een herseninfarct geregistreerd, 460 mannen (51%) en 439 vrouwen (49%) met een mediane leeftijd van 71 jaar (15-96 jaar). 287 patiënten (32%) hadden een lacunair infarct en 582 patiënten (65%) een corticaal infarct. Een kleine subgroep van 30 patiënten (3%) had een bijzondere oorzaak voor het herseninfarct. De frequentie van risicofactoren voor cerebrovasculaire aandoeningen werd vergeleken met de gehele patiëntenpopulatie, lacunaire en corticale patiëntengroep en met een controle groep zonder een symptomatische cerebrovasculaire aandoening. Vasculaire risicofactoren kwamen significant vaker voor in de gehele patiëntengroep en infarct subgroepen in vergelijking met de controle groep. Het vasculaire risico profiel voor patiënten met lacunair en corticaal infarct was gelijk. De frequentie van emboliebronnen, vanuit de arteria carotis of vanuit het hart, was echter significant lager in de patiënten met een lacunair infarct. Deze bevinding komt overeen met het inzicht dat lacunaire infarcten worden veroorzaakt door een aandoening van de kleine hersenarteriën.

In **hoofdstuk 3** werden 29 patiënten met een lacunair infarct en 30 patiënten met een corticaal infarct onderzocht op afwijkingen van de grote en kleine arteriën buiten de hersenen, met als doel om te onderzoeken of afwijkingen van de kleine arteriën exclusief gerelateerd zijn aan patiënten met een lacunair infarct. Het optreden van afwijkingen van de grote arteriën werd onderzocht met behulp van duplex scanning van de arteriae carotis en renalis en met behulp van Doppler sonografie van de grote arteriën van de benen. De kleine arteriën buiten de hersenen werden onderzocht met behulp van de retina foto's, nierperfusie scintigrafie, plasma renine bepalingen en capillaire microscopie van het nagelbed. Behoudens stenose van de arteria carotis, welke significant minder vaak aanwezig was bij patiënten met een lacunair infarct, werden er geen verschillen gevonden in het optreden van afwijkingen in de grote en kleine arteriën bij patiënten met een lacunair of corticaal infarct. Afwijkingen van de kleine arteriën buiten de hersenen zijn dus niet exclusief gerelateerd aan een lacunair infarct.

In **hoofdstuk 4** werden enige parameters van de hemostase onderzocht bij patiënten met een lacunair infarct en vergeleken met die van patiënten met een corticaal infarct, om te onderzoeken of afwijkingen in de hemostase een rol spelen in de pathogenese van lacunaire infarcten. Deze bepalingen

werden in acute fase van het herseninfarct verricht. De volgende hematologische parameters werden onderzocht: trombocyten aantal, fibrinogeen, antithrombine, proteïne C activiteit, geactiveerde proteïne C resistentie, totaal en vrij proteïne S antigeen, v Willebrand factor antigeen, lupus anticoagulant en antilichamen tegen cardiolipine. Er werden geen verschillen aangetoond in de onderzochte hematologische parameters in de acute fase van lacunaire en corticale infarcten. Fibrinogeen was in beide infarct groepen hoog-normaal. Het is dan ook onwaarschijnlijk dat afwijkingen in de hemostase een belangrijke rol spelen in de pathogenese van zowel lacunaire als corticale infarcten. De hoog-normale waarde van fibrinogeen in beide infarct groepen ondersteunt het concept dat het vasculaire risicoprofiel in lacunaire en corticale infarcten gelijk is.

Hoofdstuk 5 beschrijft HLA typering in een groep patiënten met een lacunair infarct in vergelijking met een groep patiënten met een corticaal infarct, om te onderzoeken of er een mogelijke genetische predispositie bestaat voor het krijgen van een lacunair infarct. Bij patiënten met een lacunair infarct is er een significant hogere incidentie van het HLA-B35 antigeen in vergelijking met patiënten met een corticaal infarct en een gezonde controle groep. Er werden geen significante verschillen gevonden in alle andere HLA klasse I en II antigenen. Deze bevinding toont een associatie aan tussen lacunair infarcten en HLA-B35, en suggereert een genetische predispositie voor het krijgen van een lacunair infarct. Een genetische predispositie verklaart mogelijk het ontstaan van deze aandoening van de kleine hersenarteriën in de aanwezigheid van vasculaire risicofactoren die afwijkingen van de grote arteriën veroorzaken.

In **hoofdstuk 6** werden de verschillen in oorzaken van infarcten tussen jongere en oudere patiënten met een lacunair of corticaal infarct onderzocht. Bijzondere oorzaken, zoals arteria carotis dissectie, treden significant vaker op bij jonge patiënten. Al deze jonge patiënten bleken een corticaal infarct te hebben. Verder bleek de gehele groep van patiënten met een lacunair infarct significant minder vaak een bijzondere oorzaak te hebben in vergelijking met de gehele groep patiënten met een corticaal infarct. Een belangrijke stenose van de arteria carotis en een cardiale emboliebron, zowel bij jongere als oudere patiënten met een lacunair infarct, kwam significant minder vaak voor dan bij patiënten met een corticaal infarct. Deze bevindingen ondersteunen het concept dat het lacunaire herseninfarct veroorzaakt wordt door een aandoening van de kleine hersenarteriën, ongeacht de leeftijd van de patiënt. Men kan zich dan ook afvragen of speciaal aanvullend onderzoek bij jonge patiënten met een lacunair infarct naar de oorzaak van een dergelijk infarct, zoals bijvoorbeeld angiografie, wel noodzakelijk is.

In **hoofdstuk 7** worden 3 patiënten beschreven met een geïsoleerde hemiataxie als gevolg van een lacunair infarct. Dit is een zeldzaam symptoom na het krijgen van een herseninfarct. De ataxie is klinisch van het cerebellaire type. CT en/of MRI toonde in 2 patiënten een lacunair infarct in het achterste been van de capsula interna en bij de 3e patiënt een thalamocapsulair infarct. Geïsoleerde hemiataxie veroorzaakt door een capsulair infarct is nooit eerder beschreven. De coördinatiestoornis van het cerebellaire type wordt het meest waarschijnlijk veroorzaakt door een onderbreking van de cerebellaire banen op het niveau van de capsula interna: van de opstijgende dentatorubrothalamocorticale baan of van de afdalende corticopontocerebellaire baan. Het feit dat de hemiataxie geïsoleerd voorkomt, toont aan dat de cerebellaire banen op het niveau van de capsula interna gescheiden lopen van de motorische en sensorische banen.

In **hoofdstuk 8** werd tenslotte een reeks patiënten bestudeerd met ataxie als gevolg van een lacunair infarct om de oorzaak van deze ataxie te bepalen. De patiënten werden onderzocht met klinisch sensibiliteitsonderzoek en met somatosensory evoked potentials (SEP) van de nervus medianus beiderzijds. Alle patiënten ondergingen een CT en/of MRI. De resultaten van de SEP werden bestudeerd naar een mogelijke relatie tussen klinische verschijnselen, infarct lokatie en grootte. Bij geen van de patiënten werden er klinisch aanwijzingen gevonden voor een gestoorde propriocepsis en in het merendeel van patienten waren de SEP niet afwijkend. De meeste lacunaire infarcten zijn gelokaliseerd in de capsula interna of de corona radiata. Er werd geen onderling verband gevonden tussen SEP afwijkingen, klinische verschijnselen, infarct lokatie of grootte. Deze bevindingen maken een gestoorde propriocepsis als oorzaak van de ataxie zeer onwaarschijnlijk. Onderbreking van de cerebellaire banen, de opstijgende of afdalende, op het niveau van de capsula interna of de corona radiata is meest waarschijnlijk de oorzaak van de ataxie als gevolg van een lacunair infarct.

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Curriculum Vitae

Gert-Jan Luijckx werd geboren op 14 november 1957 in Heerlen. Hij behaalde zijn Atheneum-B diploma aan het Sintermeerten College in Heerlen. Na het voltooien van de studie geneeskunde aan de Rijksuniversiteit Groningen, werkte hij gedurende driekwart jaar als arts-onderzoeker bij de werkgroep multiple sclerose van de afdeling Neurologie, Academisch Ziekenhuis Groningen (Prof.dr. J.M. Minderhoud). Vervolgens werkte hij gedurende 1 jaar als arts-assistent op de afdeling Neurologie van het ziekenhuis Gooi-Noord. In 1989 trad hij in dienst bij de afdeling Neurologie van het Academisch Ziekenhuis Maastricht, waar hij sinds juli 1990 in opleiding is tot neuroloog (Prof.dr. P.J.M. van der Lugt, Prof. dr. J. Troost). In 1993-1994 behaalde hij zijn aantekening klinische neurofysiologie (Prof.dr. F. Spaans). Na het beëindigen van zijn opleiding tot neuroloog (maart 1996) zal hij gaan werken op de afdeling kinderneurologie van het Academisch Ziekenhuis Maastricht.

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